



Spontaneous Mammary Tumor with Concurrent Cavernous Hemangioma in Albino Mice- A Rare Case Report from Mizoram, India

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ABSTRACT

Background: Mouse mammary tumor is a common neoplasm of the species. Mice is an established model for human breast cancer studies and in recent times for transgenic studies. Hemangiomas are tumors of blood vascular system. Hemangioma with breast cancer is reported in human beings. Presented study describes an unusual case of concurrent mouse mammary tumor and cavernous hemangioma from Mizoram, India.

Methods: A mortality of 8 out of a colony of 25 female albino mice was observed due to mammary tumors. Dead mice were thoroughly necropsied and tissue samples were collected from different parts of each tumor mass and fixed in neutral buffered formalin. The fixed tissues were processed for hematoxylin and eosin staining by routine paraffin embedding, microtomy and staining protocol.

Result: Gross examination revealed variable sized tumors on abdomen of affected mice. Histopathology revealed two different forms of mammary tumor viz, acinar and solid mammary carcinoma. Most peculiar finding was remarkable presence of large, endothelial lined cavernous spaces with presence of stagnant blood. These were diagnosed as cavernous hemangioma. Perusal of available literature did not reveal any report of cavernous hemangioma occurring with mouse mammary tumor, while it is found in other species including human beings.

Key words: Albino mice, Cavernous hemangioma, Spontaneous mammary tumor.

INTRODUCTION

Mouse is an important model for transgenic studies in human breast cancer. The spontaneous mouse mammary tumors arise due to Mouse Mammary Tumor Virus or chemical carcinogenesis (Cardiff *et al.*, 2000). For decades mouse mammary neoplasms had been studied in depth and out of which arose various classifications for convenience of diagnosis and research. First accepted histopathological classification of mouse mammary tumor was given by Dr. Thelma Dunn and her colleagues (Dunn, 1959) which was subsequently modified (Sass and Dunn, 1979). However with widening of knowledge sphere in this field and with advent of transgenic mice, newer and more descriptive classifications were introduced (Cardiff *et al.*, 2000). In India canine mammary tumor is one of the most thoroughly studied neoplasm as a clinical model for human breast cancer utilizing various techniques like electron microscopy to detect virus etiology (Veena *et al.*, 2013), P53 gene changes with immunohistochemistry (Veena *et al.*, 2014) and fine needle aspiration biopsy for clinical diagnosis and treatment (Gupta *et al.*, 2014). Studies in rodents like mice are inclined more towards experimental investigations especially towards novel ameliorative therapies (Adiga *et al.*, 2018).

It is not infrequent to find hemangioma with breast cancer in human beings (Kawatra *et al.*, 2009; Rajdeo *et al.*, 2015). Hemangiomas in mice are not frequently encountered and can be associated with chemical carcinogens. However, hemangioma has been experimentally induced in transgenic mice carrying the Py large T antigen (LT) gene of polyoma

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virus (Bautch *et al.*, 1987) and on treatment with radioactive compounds (Ash and Loutit, 1977). Here we report a peculiar case of spontaneous mouse mammary tumor with cavernous hemangioma.

MATERIALS AND METHODS

Animals

A mortality of 8 out of a colony of 25 female albino mice maintained for research purpose in department of Pharmacology and Toxicology of the institute was observed. All mice were of age between 3 to 3.5 months. None of the mice in the colony of 25 were pregnant during the episode or were under any experimentation.

Sampling

Initially a pea sized growth was observed around the mammary glands of the affected mice. Considering that the growth may be due to infectious etiology like mastitis or abscess, the mice were provided with antibiotic and supportive therapy through water. However, the lesions kept growing and started reaching up to the size of about 2-3 cm in a span of 10-14 days. Institutional animal ethics committee (IAEC) was approached for euthanasia of the affected mice, however, meanwhile the affected mice died natural death by 12th to 14th day.

The dead mice were subjected to necropsy examination at department of Veterinary Pathology of the institute and representative tissue samples from the observed tumor masses were collected from different regions in neutral buffered formalin (NBF) for fixation and further histopathological analysis.

Formalin fixed tissue pieces were processed for routine histopathology by paraffin embedding and hematoxylin & eosin (H&E) staining (Luna, 1968).

Ethical note

The study was conducted at Department of Veterinary Pathology on 8 female mice dying natural death during an outbreak of mammary tumors in a colony maintained at Department of Pharmacology and Toxicology, College of Veterinary Sciences and Animal Husbandry, Central Agricultural University, Selesih, Aizawl. Since there was no animal experimentation or slaughter involved, therefore there was no deviation from recommendations institutional animal ethics committee.

RESULTS AND DISCUSSION

Grossly the animals revealed poor body condition and a large growth in abdomen (Fig 1a). On necropsy examination it was found that the observed growth were solid and about 2-3cm across (Fig 1a) and had large, dark patches resembling hemorrhages (Fig 1a and b). On cutting the tumor masses there was oozing of copious amounts of dark colored blood.

The H & E stained section of the tumor revealed variable histopathological manifestations in different region. Some of the region revealed atypical acinar pattern composed of small clusters of cells organized around a small lumen. Faint evidence of secretions was also there in these acini. The cells and their nuclei revealed remarkable pleomorphism (Fig 2). This region could be classified as Dunn type-A mammary tumor with acinar pattern (Dunn, 1959; Sass and Dunn, 1979) or by Annapolis nomenclature as adenoma/carcinoma of mammary gland (Cardiff *et al.*, 2000). While in some parts the tumor parenchyma revealed solid cords of pleomorphic tumor cells with little, but generally no gland formation. The nuclei were large, extremely pleomorphic, vesicular and had multiple nucleoli (Fig 3). This region could be classified as Dunn type B tumor or solid mammary



Fig 1: a) A large tumor with remarkable blood filled patches in a dead albino mice. b) Solid tumor with large blood filled patches.

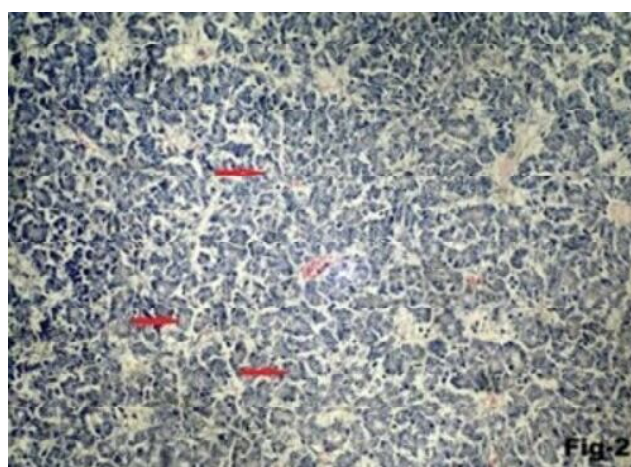
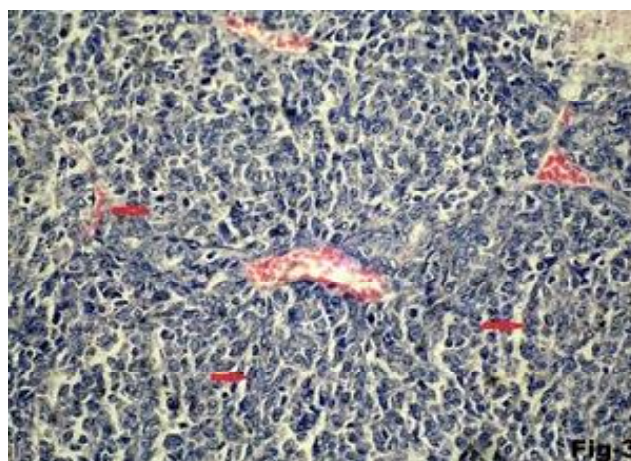


Fig 2: Mammary tumor of mice showing malformed acini (red arrow), pleomorphic tumor cells, vesicular nuclei of tumor cells, congested blood vessels, numerous pyknotic nuclei and faint pink secretions in some of the acini. (H&E, X100).



pleomorphic tumor cells with scant basophilic cytoplasm and large, extremely pleomorphic and vesicular nuclei with multiple nucleoli (red arrow). Acini formation is absent and blood vessels are congested. (H&E, X400).

carcinoma, low grade (Dunn, 1959; Sass and Dunn, 1979), while by Annapolis nomenclature it was classified as solid tumor of mammary gland (Cardiff *et al.*, 2000).

Most remarkable finding was presence of cavernous hemangioma (Fig 4 and 5). In some regions of the mammary tumor there were numerous large atypical endothelium lined cavernous spaces filled with pink staining homogenous hyaline plasma and few erythrocytes embedded in them (Fig 5). They were numerous and variable in size but all had pinkish homogenous hyaline content (plasma) with few embedded erythrocytes in them. In certain foci only a thin line of endothelium was partitioning a cavern,

The gross morphology of mammary tumor was very similar to earlier reported mammary tumor in other rodents

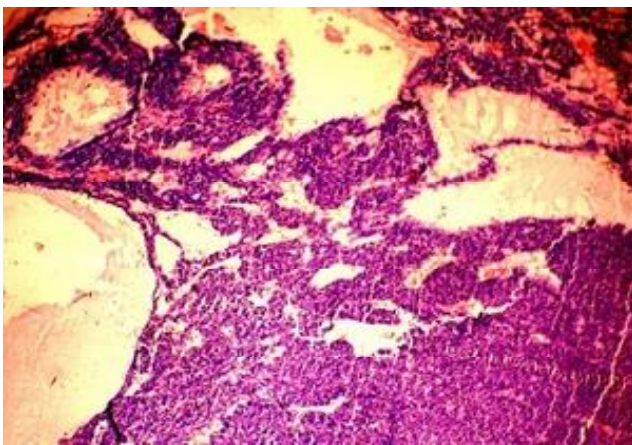


Fig 4: Numerous Cavernous hemangiomas with lining of atypical endothelial cells embedded in the parenchyma of mammary tumor. In some foci they are separated by only a thin lining of endothelial cells. There is presence of coagulated plasma and few RBC's inside the cavernous spaces indicating thrombosis (H&E, X40).

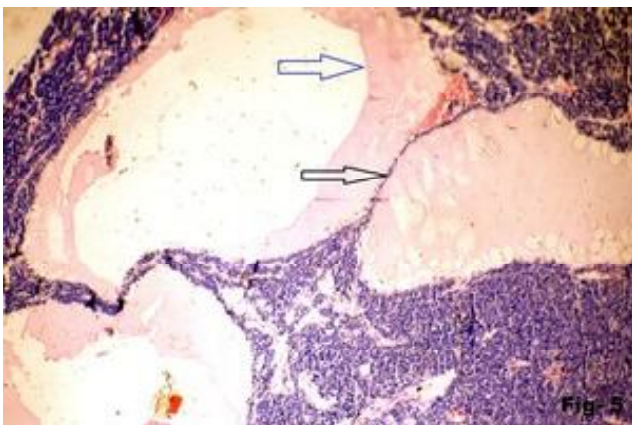


Fig 5: Cavernous hemangioma with large sinusoidal spaces which are partially lined with non-uniformly sized endothelium (black arrow). There is presence of pink homogenous plasma (Blue arrow) with embedded RBC's indicating thrombosis. Mammary tumor cells are pleomorphic with no any acinar pattern of arrangement. (H&E, X40).

(Percy and Barthold, 2007; Thangapandiya *et al.*, 2011). On histopathological analysis some parts of the mammary tumors could be diagnosed as Dunn type-A mammary tumor with acinar pattern (Dunn, 1959; Sass and Dunn, 1979) and by Annapolis nomenclature as adenoma/carcinoma of mammary gland (Cardiff *et al.*, 2000). While in some other parts Dunn type B tumor or solid mammary carcinoma, low grade (Dunn, 1959; Sass and Dunn, 1979) and by Annapolis nomenclature as solid tumor of mammary gland (Cardiff *et al.*, 2000) could be diagnosed. This finding reinforces that a single tumor mass may show variable differentiation in different parts.

Hemangioma of mammary glands with or without breast cancer have been reported in human beings (Kim *et al.*, 2006; Kawatra *et al.*, 2009; Rajdeo *et al.*, 2015). The hemangiomas are often described as 'blood blisters' especially if they are superficial. In a case of concurrent breast fibroadenoma and hemangioma in human female, they appeared as severely congested areas of brown color (Kawatra *et al.*, 2009). While in another case there was oozing of dark colored blood on attempting the biopsy (Kim *et al.*, 2006). The studied mice tumors revealed similar gross findings of large dark patches on surface like blood blisters and blood filled cavities.

A cavernous hemangioma is histopathologically characterized by large cavernous spaces filled with RBCs embedded in fibrinous matrix or coagulated plasma. The wall of the cavernous structure can be lined by a single layer of endothelial cells or sometime the cells of affected organ. The cavernous space may reveal thrombosis. Depending of duration and trauma the hemangioma shows progressive fibrosis of the walls. In later stages numerous anastomosing caverns are developed with thick fibrosed walls (Winer, 1952). Accordingly, the presented case reveals cavernous hemangioma lined with only thin layer of endothelium as earlier reported in cutaneous and ovarian tumors of human beings (Winer, 1952; Dahal *et al.*, 2018). Perusal of available literature did not reveal any report of hemangioma in mouse mammary gland, but the observed histomorphology of cavernous hemangiomas was similar to earlier published reports (Winer, 1952; Booth and Sundberg, 1995; Hardisty *et al.*, 2007; Dahal *et al.*, 2018). However, it was found that natural and induced hemangiomas in mice had been reported associated with skin, liver, pancreas, stomach, intestines, adipose tissue, sub-cutis, uterus, seminal vesicles, muscle tissue, bone marrow, spleen and cerebellum (Booth and Sundberg, 1995; Hardisty *et al.*, 2007; Kakiuchi-Kiyota *et al.*, 2013).

CONCLUSION

It could be concluded that the investigated mammary tumors had variation in grades in different regions in same tumor mass. There was also simultaneous presence of cavernous hemangioma in the tumor mass. The concurrent occurrence of mammary tumors with cavernous hemangioma is a rare finding. The observations are consistent with findings of other

workers. The present study contributes to scientific knowledge about mice mammary tumors.

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Disclaimer

As there was no animal experimentation or slaughtering in the present study therefore approval of animal ethics committee was not required. However, there was no deviation from rules of ethical treatment to animals in any part of the study.

Sources

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Statement of conflict of interest

The authors declare that they have no conflict of interests neither financial nor personal.

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