



Short communication

A spontaneous high-grade undifferentiated mammary carcinoma in a seven-week-old female rat



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ABSTRACT

The present work describes a rare case of a spontaneous high-grade carcinoma in a seven-week-old Sprague-Dawley female rat that had been included in the control group of an assay of mammary carcinogenesis. The mass was detected at 50 days of age, it grown quickly and the animal was humanely sacrificed eight days later. The tumor was located in the left cervical region, in the vicinity of the left submandibular and sublingual glands. It was soft and reddish and had several dens with a bloody content. The tumor was PAS negative and exhibited immunostaining for ER- α . The histopathologic and immunohistochemical data are suggestive of a high-grade carcinoma from mammary gland. It was the first report of a spontaneous mammary tumor in such a young rat.

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1. Introduction

There are some reports of spontaneous mammary tumors in laboratory animals. The most frequent spontaneous tumors found in Sprague-Dawley rats are adenoma of the pituitary gland, lymphoma, and mammary fibroadenoma and adenocarcinoma (Son and Gopinath, 2004). However, the tumor development is age-related, being rare the development of spontaneous tumors during the first year of life (Son and Gopinath, 2004).

2. Materials and methods

2.1. Animals

Thirty-six Sprague-Dawley female rats with four weeks of age were acquired from Harlan Interfauna Inc. (Barcelona, Spain) for

use in an assay of mammary carcinogenesis. Animals were handled according to the National and European legislation (European Directive 2010/63/EU and National Decree-law 113/2013). Procedures were approved by the Portuguese Ethics Committee for Animal Experimentation (*Direcção-Geral de Alimentação e Veterinária*, Approval no. 008961) and by the Ethics Committee of UTAD (CE_12-2013). Animals were housed at the facilities of the UTAD in filter-capped polycarbonate cages under controlled conditions of temperature ($23 \pm 2^\circ\text{C}$), humidity ($50 \pm 10\%$), air system filtration (10–20 ventilations/h) and on a 12-h:12-h light:dark cycle. A basic standard laboratory diet (4RF21, Mucedola, Italy) and tap water were supplied *ad libitum*. Animals were maintained in quarantine during one week, after this they were randomly divided into five experimental groups and they were allowed to acclimate to laboratory conditions for two weeks. Animals were observed twice a day in order to check their health status.

3. Results

3.1. Macroscopic examination

During the quarantine and acclimatization period no alterations were found. However, at 50 days of age, it was detected a movable

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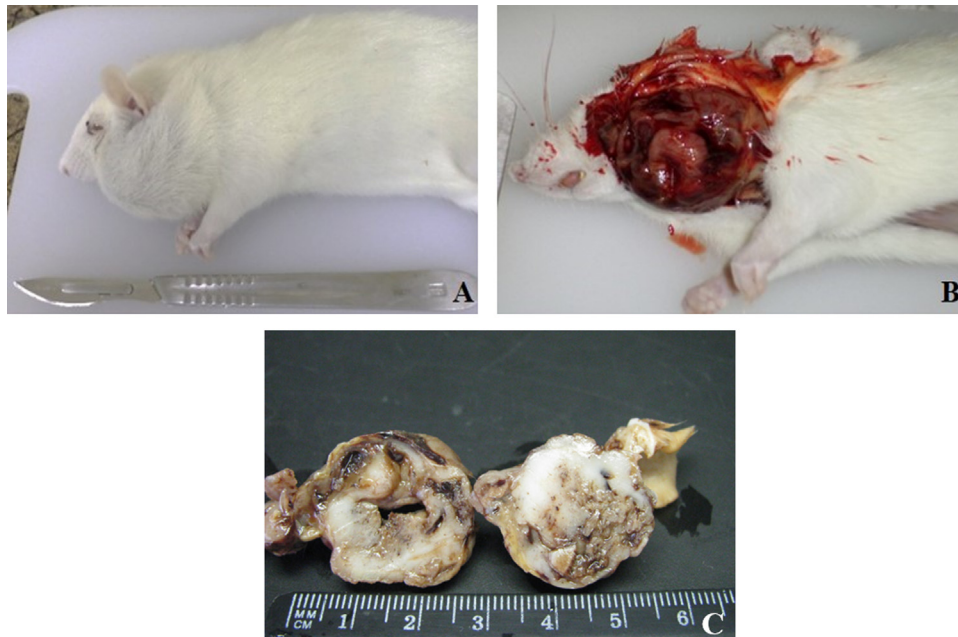


Fig. 1. Macroscopic appearance of mammary tumor before (A) and after (B and C) necropsy. Cut surface of mammary tumor after fixation exhibiting soft brown and firm white tissues (C).

mass in the left cervical region, in the vicinity of the submandibular and sublingual gland, of an animal from control group. The animal was transferred to an isolated cage. The mass grown quickly, being soft at palpation (Fig. 1A). The animal exhibited weight loss, orthopedic position, lack of grooming, chromodachryorrhea and its eyes were partially closed. Eight days after the mass detection, at 58 days of age, the animal was humanely sacrificed by intraperitoneal overdose of pentobarbital sodium (Eutasil, CEVA, Portugal). A complete necropsy was performed. The mass presented an irregular and reddish surface with several cysts filled with a bloody content, and $3.0 \times 2.5 \times 2.5$ cm in size (Fig. 1B). The mass was collected and fixated in 10% buffered formalin for 24 h. After fixation, the cut surface exhibited soft brown and firm white tissues, with a cystic central area (Fig. 1C). The remaining organs did not exhibit any alteration.

3.2. Microscopic examination

After fixation, the mass and all organs were routinely processed for histological analysis; $2 \mu\text{m}$ sections were stained with hematoxylin and eosin (H&E) and posteriorly evaluated by a pathologist. Additionally, sections of the mass were stained with periodic acid-Schiff (PAS) and immunohistochemically evaluated by staining with the primary antibody against estrogen receptor (ER)- α (clone 6F11, Novocastra, Newcastle, UK) using the standard protocol of Novolink Polymer Detection System (Leica Biosystems, UK). The antibody was incubated at a dilution of 1:50 for one and half hour at room temperature.

At the histopathological analysis, the tumor was classified as a high-grade undifferentiated carcinoma originated in the mammary gland (Fig. 2A). The tumor presented a cystic central area (Fig. 2B). It was densely cellular with the cells organized in solid nest-like structures, with comedo type carcinoma areas and scarce stroma (Fig. 2C). The tumor was vascularized with several necrotic centers (Fig. 2D). The neoplastic epithelial cells exhibited a basophilic cytoplasm with round to oval nuclei and a high mitotic index (from one to sixteen atypical mitosis *per* high power field) was observed (Fig. 2E). Stromal invasion associated with

desmoplasia was also observed (Fig. 2F). The tumor was negative for PAS staining, while the adjacent salivary gland was PAS positive (Fig. 2G and H). At the immunohistochemical analysis, some neoplastic epithelial cells and ductal epithelial cells showed a nuclear immunolabelling for ER- α (Fig. 2I–K). The adjacent salivary gland was ER- α negative (Fig. 2L). No histological alterations were found in the other organs.

4. Discussion

Sprague-Dawley rats have been frequently used in experimental assays of toxicity and carcinogenesis. However, the existing data about the occurrence of spontaneous tumors at early ages in these animals are rare (Ikezaki et al., 2011). According to the available literature, the youngest age at which a spontaneous mammary tumor was described in a Sprague-Dawley female rat was 10 weeks (Oishi et al., 1995). Recently Kuzutani et al. described a spontaneous mammary tumor in a female rat from the same strain with 12 weeks of age (Kuzutani et al., 2012).

Previous studies have reported that ER- α is expressed in the pituitary, ovary, uterus, testis, prostate, epididymis, kidney, adrenal gland, and in the epithelial cells of the normal mammary gland and in mammary tumors. In this case, some neoplastic cells were positive for ER- α . Additionally, the tumor was negative for PAS staining, which would not be expected in a tumor from salivary gland. Since the tumors of the salivary gland occur in the same anatomical location, tumors with origin in these organs such as mammary analogue secretory carcinoma of the salivary gland were considered for differential diagnosis. However, on the basis of the findings, the tumor was diagnosed as a high-grade undifferentiated carcinoma with a probable origin in the mammary gland.

To our knowledge, this is the first report describing a spontaneous mammary tumor in a Sprague-Dawley rat with an age lower than 10 weeks. No previous reports had described a spontaneous mammary tumor in such a young rat. It is important to note that our team have used a high number of Sprague-Dawley female rats in studies of carcinogenesis in the same environmental conditions (fifty and thirty-six animals were used in the first and

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