Open Veterinary Journal, (2023), Vol. 13(9): 1223-1227
ISSN: 2226-4485 (Print)
ISSN: 2218-6050 (Online)

Case Report
DOI: *10.5455/OVJ.2023.v13.i9.19*

Submitted: 25/03/2023 Accepted: 25/08/2023 Published: 30/09/2023

A spontaneous ovarian teratoma in an FVB/n female mouse: Case report and literature review

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Abstract
Background: Teratomas are rare types of germ cell neoplasms composed of various differentiated or undifferentiated tissues.
Case Description: A 25-week-old female control FVB /n mouse in a 4-week toxicity study presented abdominal distension and poor body condition. It was euthanized, and the necropsy examination revealed a large mass connected to the tip of the right uterine horn, occupying the entire abdominal cavity. Microscopically, this mass showed areas of epidermal differentiation, with laminated keratin and sebaceous glands, differentiation into respiratory and digestive epithelium, cartilage, bone, and extensive areas of differentiation into the nervous tissue, being classified as an ovarian teratoma.
Conclusion: As far as authors know, the occurrence of ovarian teratomas in the FVB/n mouse strain has never been previously described.
Keywords: Mouse, Ovary, Rodent, Teratoma.

Introduction

Mice and rats make up approximately 95% of all laboratory animals, making the mice the most used animals in biomedical research (Hickman *et al*., 2017). The analysis of the published works regarding the development of spontaneous tumors in laboratory animals, particularly in the mouse, reveals their low incidence. These values may result from two different situations: either the incidence of spontaneous tumors is very low, or many small or microscopic tumors are not identified because tissues are not collected by routine. As a standard procedure, our research team performs a complete necropsy of all animals that die during experimental trials or those must be sacrificed before the scheduled date (due to humane endpoints). Thus, with the support of experienced pathologists, we have identified several undescribed tumors in rodents, such as a Zymbal tumor in a male Wistar rat (Faustino-Rocha *et al*., 2023) and a Schwannoma in a female Sprague–Dawley rat (Teixeira-Guedes *et al*., 2014). According to Gopinath (1994), the incidence of tumors in control animals during experimental protocols is influenced by the pathologist's experience. From our perspective, the incidence of spontaneous tumors in laboratory animals

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is also associated with the perspicacity of researchers and animal caretakers. Thus, we recommend that all animals in experimental trials, regardless of the cause of their death, should constantly be subjected to a careful and complete necropsy, and their organs should be analyzed by an experienced pathologist. With this approach, we will be able to understand the rate of spontaneous tumors in laboratory animals. Although spontaneous tumors are rare in laboratory animals, it is important to obtain data about their occurrence during their life, because spontaneous tumors observed before the end of a study may avoid a misinterpretation of the data (Son and Gopinath, 2004). Herein, for the first time, we describe a case of a spontaneous teratoma in a female FVB/n mouse.

Case Details

Animals

Twenty female, 25-week-old FVB/n mice were used in a toxicity study for the safety assessment of a natural compound, the hydroethanolicc French Lavender extract (data not published). This animal belonged to the control group and was not exposed to the extract. These mice were housed in polycarbonate cages, under controlled conditions of *humidity (50% ± 10%), temperature (23°C ± 2°C), air system filtration (10–20 ventilations/hour), and on a 12/12 hours light/dark cycle,* and were allowed free access to standard laboratory diet *(4RF21, Mucedola, Italy)* and tap water. During the experimental assay, animals were observed and handled daily. On abdominal palpation, a large mass was detected in the abdomen of one mouse; its body weight was 50.1 g, while the average body weight of the other females was 25.2 g. The animal exhibited poor body condition, and, considering our humane endpoints, it was sacrificed by anesthetic overdose. The animal was subsequently subjected to a careful postmortem examination.

Gross pathological examination

During the necropsy, a large mass connected to the right uterine horn was observed, occupying the entire abdominal cavity, measuring 5.5 × 3.5 × 2.8 cm in its largest dimensions and weighing 20.6 g (Figs. 1 and 2). This mass consisted of multiple cysts, the largest measuring 2.8 × 2.0 cm, with brownish content, and small whitish solid areas. The contralateral ovary showed no macroscopical alterations. The stomach was atrophied by compression, and the remaining organs did not show significant changes. The mass and all organs were fixed in 10% buffered formalin for 24 hours for histopathologic examination.

Histopathological examination

The specimens were processed for a routine histopathology examination. After sample fixation, they were cut using a microtome. Histological sections were then prepared and stained with hematoxylin and eosin (H&E).

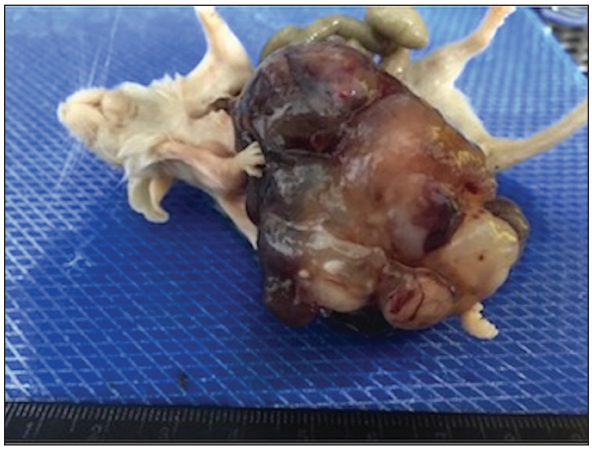

Fig. 1. Large cystic mass occupying the entire abdominal cavity.

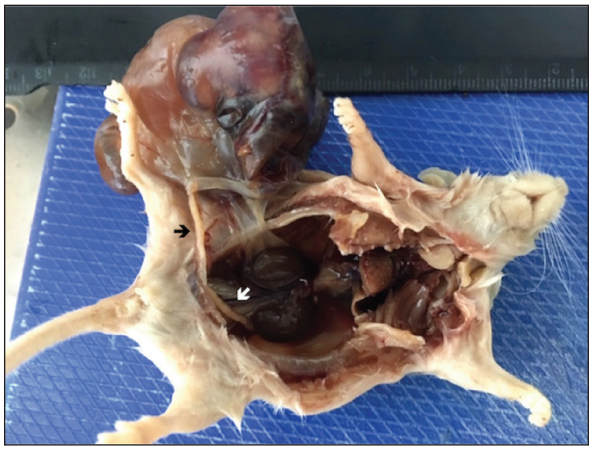

Fig. 2. Mass attached to the right uterine horn (black arrow); white arrow shows left uterine horn.

The mass presented areas of epidermal differentiation with laminated keratin and sebaceous glands. Cell differentiation into digestive and respiratory epithelium, bone, cartilage, and vast areas of differentiation into nervous tissue were also present (Figs. 3–7). Moreover, the nervous tissue presented focal areas of ependymoma. Epithelial areas with hypercellularity, cell atypia, stromal microinvasion, hemorrhages, and necrosis were also observed. Metastatic epithelial cells were detected invading the pancreas, the small intestine serosa, and the mesenterium. Therefore, the mass was classified as a malignant teratoma with abdominal carcinomatosis.

Ethical approval

All animals were carefully handled following the European Guidelines for experimental studies (National Decree-law 113/2013 and European Directive 2010/63/EU). The study was approved by the National Competent Authority and by the University Ethics Committee.

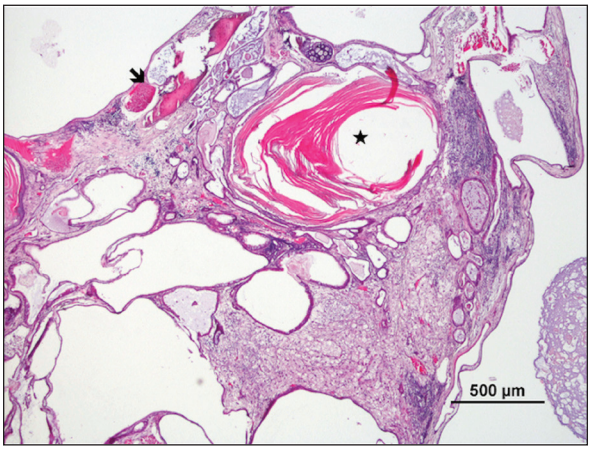

Fig. 3. Cystic mass with differentiation into stratified epithelium with accumulation of laminated keratin (*) and bone (arrow) (H&E).

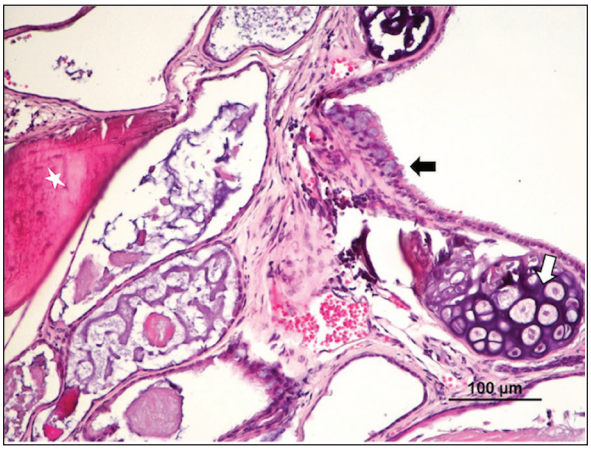

Fig. 4. Bone (*), cartilage (white arrow), and respiratory epithelium (black arrow) (H&E).

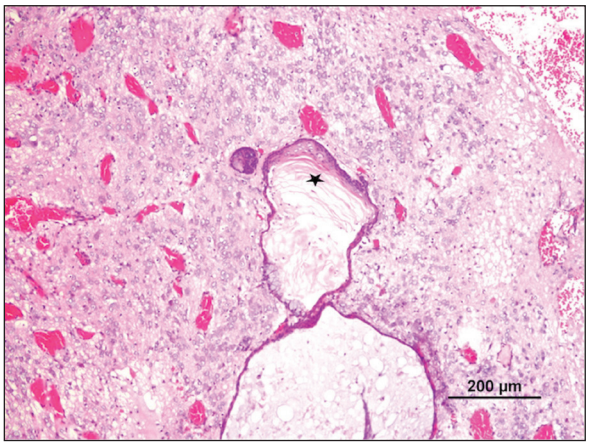

Fig. 5. Keratinized epithelium with an accumulation of laminated keratin (*), surrounded by well-differentiated nervous tissue (H&E).

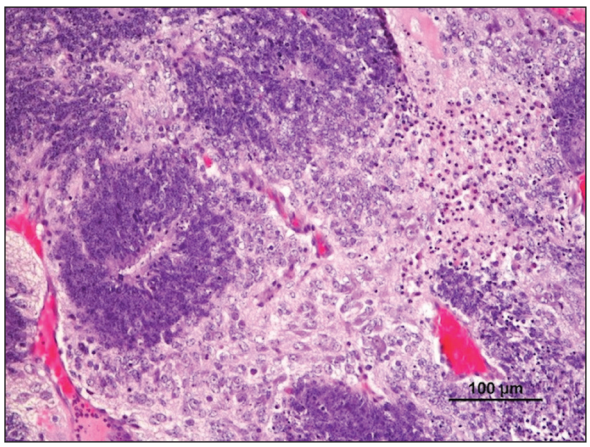

Fig. 6. Ependymoma (H&E).

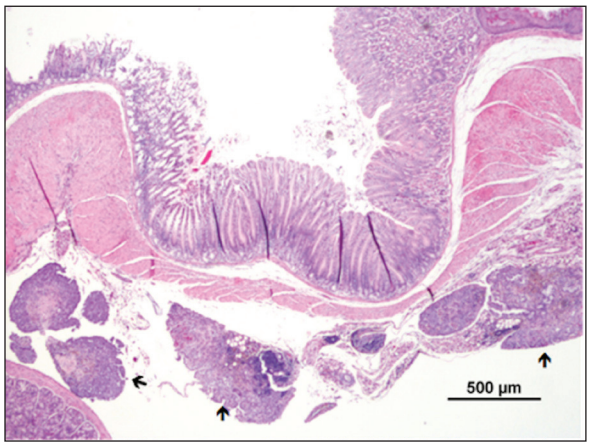

Fig. 7. Metastasis on gut serosa ( ) (H&E).

Discussion

The word "teratoma" is derived from the Greek word "teraton," meaning monster, and it was coined by Virchow in 1863 (Comerci *et al*., 1994). Teratomas are complex neoplasms arising from more than one embryonic germ layer, composed of a variety of unorganized, differentiated, or undifferentiated tissues originating from ectoderm (hair, teeth, and nervous tissue), mesoderm (fibrous or adipose tissue, bone, muscle, and cartilage), and endoderm (respiratory tissue and salivary gland) (Sirivisoot *et al*., 2022). Most teratomas arise in the gonads, though occasionally, they may develop in extragonadal sites, such as the anterior mediastinum, retroperitoneal, and gastrointestinal tract. Extragonadal teratoma develops from primordial germ cells misplaced during their migration to gonads (De Felici *et al*., 2021; Sirivisoot *et al*., 2022).

Two types of teratomas have been described: mature and immature. The mature teratoma is frequent, representing 50% of all ovary tumors, while the immature ones are scarce, representing only 1% (Saba *et al*., 2009). According to the ratio between dedifferentiated or

incompletely differentiated and well-differentiated cell populations, biological behavior might range from benign to malignant (Sirivisoot *et al*., 2022). Mature teratomas are usually benign, but in 0.1%–0.2% of cases, they may undergo malignant transformation (Giustini *et al*., 1978).

Teratomas are rare lesions in domestic animals. Nevertheless, gonadal teratomas are more common in bitches (Agnew and MacLachlan, 2016) and guinea pigs (Barthold *et al*., 2016), but rarely documented in other species, such as horses (Lefebvre *et al*., 2005), heifers (Carluccio *et al*., 2017), and cats (Sirivisoot *et al*., 2022). Considering laboratory animals, ovarian teratomas were defined as very rare in female rats (Tsubota *et al*., 2004). The first ovarian teratoma in mice was described by Slye *et al*. (1920). Afterward, ovarian teratomas were identified in a C3H female mouse by Jackson and Brues (1941); in Swiss albino mice by Fawcett (1950); and in C3HeB mice by Fekete and Ferrigno (1952). Thiery (1963) reported two cases of ovarian teratoma in C3H/N mice occurring in his colony: the first was identified in a 6-month-old breeding mouse and the second was reported in a virgin mouse. In this last case, the uterine cervix had been painted twice a week for 18 weeks with a 1% suspension of 3,4-benzopyrene in acetone to induce cervicovaginal cancer and had ingested 0.8 mg of estriol. According to Stevens and Varnum (1974), between 1920 and 1974, nine cases of teratomas were described in the following mice strains: C3H, Swiss Albino, C3HeB, C3H/N, CBA/J, and DBA/2J. Considering how relevant this tumor is in obstetrics and gynecology medicine, these researchers tried to develop an animal model to study ovarian teratoma in the LT mouse strain. However, ovarian teratomas of LT female mice were benign and composed of multiple types of well-differentiated tissues of embryonic and extraembryonic origin (Stevens and Varnum, 1974). Damjanov *et al*. (1975) described ovarian teratomas from 8, 9 to 10-week-old mice from a large colony of LT mice. Tumors were unilateral in all animals, except for one case that presented bilateral teratomas. In 1987, an analysis of the incidence of ovary teratoma in the B6C3F1 female mice was made and an incidence of 13.8% was reported (Alison and Morgan, 1987). More recently, Naser *et al*. (2021) crossed LT-*ett1* and a previously established LT-*Ter* strain to develop the double-congenic strain LT-*Ter-ett1*. Furthermore, they also found a strain with a point mutation in the *MC4R* gene of the LT strain by genome editing, LT-MC4R^{G25S}, and developed a double genetically modified strain LT-Ter-MC4R^{G25S} to address the relation between *Ter* and *MC4R* genes. They observed the development of ovarian teratomas in all strains and concluded that *MC4R* is one of the genes responsible for forming ovarian teratomas (Naser *et al*., 2021).

Although some reports of spontaneous ovarian teratomas in several strains of laboratory mice have appeared in the literature over the years, no reports were found in FVB/n mice. In the present case, for the first time, an ovarian teratoma was identified in a female laboratory FVB/n mouse, consisting of tissues originating from the three embryonic layers (endoderm, mesoderm, and ectoderm). The presence of invasive neoplasia and peritoneal carcinomatosis lesions confirms its malignant character. Though metastasis is rare, intra-abdominal metastasis was also reported to be associated with immature cat teratomas (Sirivisoot *et al*., 2022).

Acknowledgment

None.

Conflict of interest

The authors declare that they have no conflict of interest.

Author contributions

Paula A. Oliveira performed the experimental design, supervised the animal experiments, participated in animals' sacrifice, and wrote the manuscript; Rui M. Gil da Costa made the histopathological diagnosis and wrote the manuscript; Elisabete Nascimento-Gonçalves conducted experiments with live animals and wrote the manuscript; Ana I. Faustino-Rocha conducted experiments with live animals and wrote the manuscript; Ana Margarida Calado made the histopathological diagnosis and wrote the manuscript; Adelina Gama made the histopathological diagnosis and wrote the manuscript; Catarina Jota Baptista wrote and revised the manuscript; Fernanda Seixas participated in animals' sacrifice, made the histopathological diagnosis and wrote the manuscript.

Funding

This work was supported by National Funds by the Portuguese Foundation for Science and Technology (FCT). The authors of the research unit CITAB received funding from FCT; reference of the projects UIDB/04033/2020 and LA/P/0126/2020. The authors of the research unit CECAV received funding from FCT; reference of the projects UIDB/CVT/00772/2020 and LA/P/0059/2020. ENG thanks FCT/MCTES and European Social Funding (EFS) through NORTE2020 for her Ph.D. fellowship grant ref. SFRH/BD/136747/2018. CJB is grateful to FCT for her Ph.D. grant (202104520.BD).

Data availability

All data supporting the findings of this study are available within the manuscript. Any extra data needed are available from the corresponding author upon reasonable request.

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