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**First report of granulosa cell tumour associated with an endometrial adenoma in a crossbreed cow in Portugal**

**D. Moura<sup>1</sup>, J. García-Díez<sup>2\*</sup>, C. Saraiva<sup>2</sup>, M.A. Pires<sup>2</sup>**

<sup>1</sup>*North Division of the Portuguese Food and Veterinary National Authority (DSAVRN).*

*Portuguese Food and Veterinary National Authority (DGAV). Portugal.*

<sup>2</sup>*CECAV – Animal and Veterinary Research Centre. University of Trás-os-Montes e Alto Douro, Portugal.*

**ABSTRACT.** A 12.5 year-old female crossbred cow without clinical signs at ante mortem inspection was slaughtered. The post-mortem inspection revealed poor carcass condition, interstitial nephritis and generalized lymphadenitis. The reproductive tract presented an unilateral and highly vascularized yellowish-white mass, with huge dimensions (60 x 40 cm and 20 Kg, approximately) described as granulosa cell tumour (GCT) and a endometrial adenoma, after histopathological analysis.

GCT has been described as the most frequent ovarian tumour in cattle. Since clinical signs are usually unspecific, the post mortem diagnosis by histopathology examination is always necessary. The endometrial adenoma could be asymptomatic, with only absence of calving, or associated with GCT. This is, of our knowledge, the first report of a GCT associated with endometrial adenoma in a cow in Portugal.

**Keywords:** granulosa cell tumour, ovary, endometrial adenoma, cattle

*Corresponding Author:*

Juan GarcíaDíez, DVM, MSc, PhD  
1CECAV – Animal and Veterinary Research Centre. Universityof Trás-os-Montes e Alto Douro, Quinta de Prados, 5000-801 Vila Real, Portugal  
Email: juangarciadiez@gmail.com

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## INTRODUCTION

Granulosa cell tumour (GCT) has been described in cattle (Anderson et al., 1969, Bosu, 1977, Hosteller et al., 1997, Leder et al., 1988) as well in other species (Kennedy et al., 1998, Patnaik et al., 1987). Although tumours in cattle are scarce (Garcia-Iglesias et al., 1995), GCT is considered as the most common ovarian tumour of this species (Agnew and MacLachlan, 2017) Kennedy et al, 1998; Farin, 1993). GCT affects all breeds of cattle but implementation of reproductive programs in dairy herds may explain its higher incidence compared to beef cattle. Clinical signs are variable but commonly the condition involves reproductive disorders, in consequence of hormonal production. In some cases, a presumptive diagnosis is made based on clinical signs and rectal palpation, mainly when an ovary presented an abnormal size compared to the contralateral one, that is in most cases atrophied (Bosu, 1977). However, ultrasonography may improve the presumptive diagnosis in live animal.

Despite tumours mainly occur in older animals, some cases are reported in younger as two years (Short et al., 1963) or 9 months (Masseau et al, 2004).

Endometrial adenoma is a very rare condition in domestic animals as its malignant counterpart is considered more common in cow (Kennedy et al, 1998). Recently reports consider this situation in cat more common than described before, and proposed to be related with hormonal dysregulation with influence of progesterone in this tumour (Payan-Carreira et al., 2013, Saraiva et al., 2015). The presence of concomitant pyometra (with the presence of a purulent exudate) is reported in a high number of adenocarcinomas in the cat (Pires et al., 2016).

The livestock management in which cattle are slaughtered after a few months of growth difficult the diagnostics of similar situation. Thus, most tumour lesions are observed in the slaughterhouses after meat inspection (Lucena et al., 2011). We intend to highlight the importance of its macroscopic diagnosis since presence of tumours lesions during meat inspection implies the whole carcass condemnation.

## CASE DESCRIPTION

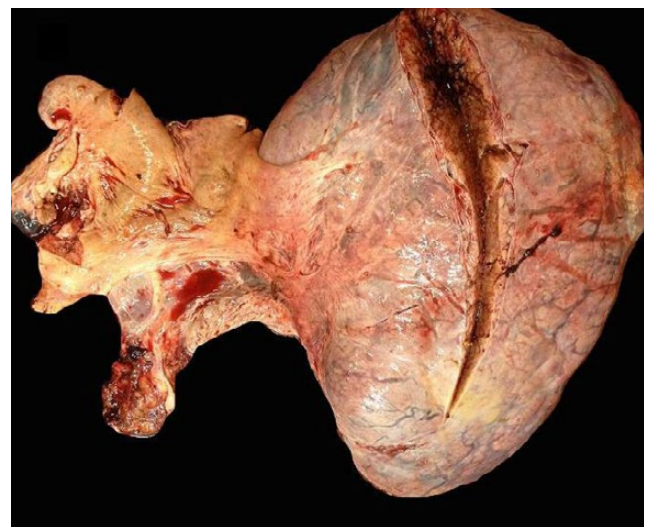
A 12.5 year-old female crossbred cow was slaugh-

tered intended for human consumption without clinical signs at ante mortem inspection. The cow health record registered in the Portuguese National Cattle Database indicated 9 calving being the last one three years ago and 16 official screenings for bovine tuberculosis and brucellosis diagnostics with negative results. The compulsory food chain information form presented by the owner to the meat inspector not registered any clinical information regarding the cow.

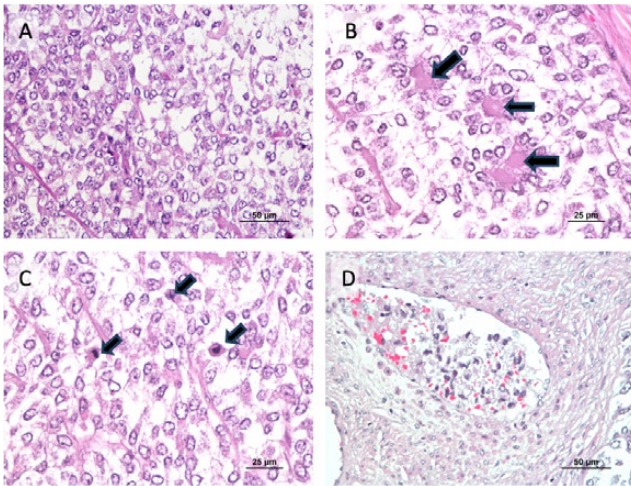
## RESULTS

The post mortem inspection revealed cachexia, whitish muscle and generalised lymphadenomegalia. The visual inspection of the offal revealed the presence of white-spotted lesions on the surface of both kidneys, and the inspection of the reproductive tract revealed a unilateral, highly vascularized, yellowish-white mass, with huge dimensions (60 x 40 cm and 20 Kg, approximately), compatible with an ovarian neoplasia presented in the right side (Figure 1). The left ovary does not present any macroscopic alteration. The cut surface presented a solid yellow mass with haemorrhagic and necrotic areas. Also, it presented macroscopic unspecific uterine lesions. According to the multi-location of the lesions, the carcass was condemned by meat-inspectors.

Samples of kidneys, lymph nodes, ovary and uterus



**Figure 1.** Enlarged right ovary transformed in a single yellow mass. Some haemorrhagic and necrotic tissues are seen in the cut surface. Note the atrophic aspect of the contralateral ovary.



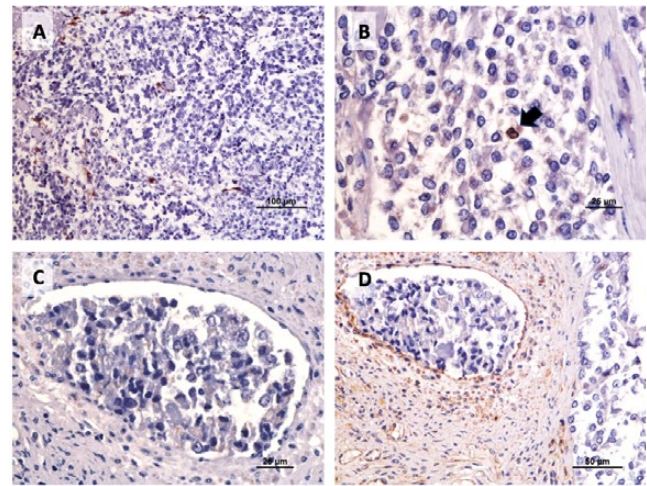
**Figure 2.** Histological images of the right ovary. A – Presence of granulosa cells in diffuse and solid pattern. The cells are pleomorphic with dense or vesicular nucleus, distinct nucleoli, with eosinophil or vesicular clear cytoplasm. B – Some cells are distributed in a microfollicular pattern (Call-Exner bodies, arrow) with hyaline eosinophil material inside a rosette like arrangement. C – Some mitoses isseeming (arrow) some of them anomalous. D –Vascular invasion of granulosa cells. Haematoxylin and Eosin staining.

were collected for histopathological analysis. All tissues were fixed in buffered 10 % formalin and routinely processed and embedded in paraffin wax. Sections of 3- $\mu$ m thick were stained with haematoxylin and eosin (HE).

Ovary samples were 3- $\mu$ m thick sectioned to Silane® coated slides and performed immunohistochemistry by the indirect avidin-biotin peroxidase complex technique, with the antibodies anti-vimentin (NCL-L-Vim-V9, Novocastra, 1:100 dilution); broad spectrum keratin (clone AE1/AE3, Dako®, Denmark, 1:50 dilution) and Ki67 (clone Mib-1, Dako®, Denmark, 1:50 dilution).

The histological evaluation of the kidney revealed the presence of interstitial infiltrate by mononuclear inflammatory cells, with hyaline cylinders and calcium in the pelvis, small cystics of distinct dimensions and fibrosis in the cortex corresponding to an old infarct, classified as interstitial chronic nephritis.

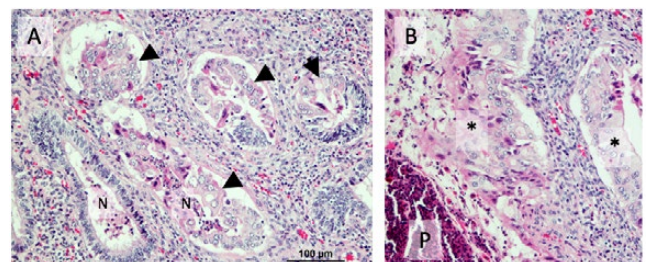
The ovary presented intense proliferation of fusiform cells with eosinophilic to vesicular/clear cytoplasm in a tubular to diffuse (and solid) pattern. Also,



**Figure 3.** Immunohistochemical labelling of the granulosa cell tumour. A – Broad spectrum keratin showing a sporadic cytoplasm positivity. B - Ki67 positive nucleus (arrow). C- Cluster of CGT with weak and sporadic positivity to a broad-spectrum keratin inside a vessel. Serial section of that fig. 2D. D – Vimentin sporadic positivity of GCT cells, inside a vessel. Serial section of that fig. C. Gill's haematoxylin counterstaining.

cell's nucleus was vesiculated or dense and presented evident nucleolus (Figure 2 A and B). Necrosis and images of vascular invasion of neoplastic cells and low mitotic rate (one to two mitotic figures per high microscopic field-HPF- 40x, Figure 2 C, D and E).

At immunohistochemistry evaluation, rare cells were positive to vimentin and to broad spectrum keratin, and above 1% of Ki/67positive count (Figure 3 A and B). Images of vascular invasion are evidenced



**Figure 4.** Images of endometrial adenoma. A - Observe the presence of neutrophils (N) inside endometrial glands (normal or with atypia - arrow). B –Presence of cellular atypia of the glands (\*), purulent exudate with neutrophils and debris (P). Haematoxylin and eosin staining.

by weak positive to keratin cells inside vessels and vimentin positive vessels walls (Figure 3 C and D).

According to the morphological aspects of the lesion, it was classified as malignant granulosa cell tumour.

The endometrium presented cystic hyperplasia of glands, with neutrophil infiltrate in some cases. In addition, some of these glands presented moderate cytological atypia, clear nucleus, loss of nucleus polarity, some binucleated cells, that was compatible with an endometrial adenoma (Figure 4A and B).

The histopathological analysis of iliac lymph node revealed the presence of germinal centres, eosinophils, neutrophils and increased number of plasma cells in its medulla corresponding to hyperplasia and lymph node reactivity. No neoplastic cells were evident inside this lymph node.

## DISCUSSION

Granulosa cell tumours (GCT) are specific lesions of the ovary. Although its aetiology is not completely described, some genetic mechanisms and further hormone disruptions could be involved on its development (Kitahara et al., 2012). In animals, CGC have been described both in companion animals (Panaitk, 1987) and farm animals (Anderson et al., 1969, Kennedy et al., 1998). Adenoma of the endometrium is also described as rare entity in domestic animals (Kennedy et al., 1998).

In the consulted literature, the authors did not find the association between GCT and endometrial adenoma in cattle, and the best of our knowledge, this is the first case reported in Portugal.

GCT was described in cattle over 10 years (Bosu, 1997) in accordance with the present case. However, cases in young cattle with less than 4 years and also a case in a 9 months' calf have also been described (Hosteller et al., 1997, Kanagawa et al., 1964, Leder et al., 1988, Masseur et al., 2004, Zachary et al., 1983).

Clinical signs of GCT in cattle are variable although most of them remain asymptomatic. The cachexia and generalised lymphadenomegalia observed are unspecific clinical signs related with malignant neoplasms, in which its relationship with the GCT is not clear, but could be related with the

neoplasia products released or its (huge) dimensions that could make pressing in the digestive tract and in abdomen. However, presence of dorsal jerking of the head, excessive salivation, abnormal udder development, nymphomaniac behaviour, infertility or abnormal findings by transrectal palpation or ultrasonography have been described as clinical signs related with GCT.

The diagnosis of GCT in live cattle is not frequent and usually associated to the identification of compatible images at ultrasonography in routine pregnancy diagnosis (Dobson et al., 2013). Although fine-needle aspiration or endocrine analysis are also recommended (Hosteller et al., 1997), the histopathological analysis is essential for a definitive diagnosis. In the present case, the diagnosis was performed after post mortem inspection due to the absence of clinical symptomatology. However, the absence of calves' registration on national cattle database suggested infertility in the last three years could be related with this tumour development as with the lesions found in the uterus.

In cases of absence of clinical symptomatology, a careful post mortem examination at necropsy or slaughterhouse inspection have been described as the only way to observe the tumour or other lesions (Kanagawa et al., 1964).

A variable size of the granulosa cell tumours, bilateral presentation and presence of metastasis are the most important features described in the literature (Kanagawa et al., 1964). GCT are malignant tumours and report of metastasis is not common (Patnaik, 1978). However, Zachary and Haliburton (1983) reported metastasis on the peritoneum and the liver. The case studied only presented a large-sized unilateral tumour with histologic evidences of neoplastic cells vascular invasion but without evidence of metastasis in the regional lymph node or in any other organs observed. The hormonal dysregulation with production of steroids by this CGT could be related to the endometrial adenoma found in the uterus as proposed by other authors (Payan-Carreira et al., 2013, Saraiva et al. 2015) and both situations should be responsible for the absence of calving in the last 3 years.

Regarding treatment, surgical removal and medical management has been described (Dobson et al., 2013)

for GCT but its successful could be conditioned by the location and size of the tumour. Since the economic cost of the treatments is not compensatory, the affected cattle are usually destined for slaughter. Nevertheless, in the present case, the endometrial adenoma, not clinically identified, will reduce the fertility even after ovarian removing.

In conclusion, this is the first case description of CGT associated with an endometrial adenoma in a cow, in Portugal, that highlights the essential role of the meat inspector at the slaughterhouse in the evaluation of macroscopic tumour-like lesions that could lead, as in the present case, to the carcass condemna-

tion after histopathological confirmation.

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#### **CONFLICT OF INTEREST STATEMENT**

The authors declare no conflict of interest. ■

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