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Original article

Adrenal gland tumors in dairy cattle from Northern Italy: morphological and phenotypical characterization in comparison with human pathology

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Abstract

Bovine adrenal gland tumours are considered relatively common, although scarce data are available about their real incidence, pathological characterization, classification criteria and immunohistochemical profile. This study describes the morphological and immunophenotypical characteristics of 35 dairy cattle adrenal gland tumors from Northern Italy and compare them with human pathology. Macroscopical, histological, histochemical and immunohistochemical investigations were performed. Microscopically proliferative lesions were classified as focal hyperplasia (8/35), primary cortical tumors (15/35) , primary medullary tumors (12/35). The cortical tumors showed a highly heterogeneous spectrum of morphological aspects not matching the two major diagnostic categories of adenoma and carcinoma in either cattle or humans. The medullary tumors (7 neuroblastomas and 5 pheochromocytomas) showed morphological and immunophenotypical features largely overlapping with human counterparts. Although limited by the small number of neoplasms and the lack of evidence of metastases precluding a clear distinction between benign and malignant lesions, this study represents the first attempt to compare the bovine and the human pathology. The present data support the concept that adrenal tumors in cattle have distinctive features that deserve a species-specific classification.

Key words: adrenal gland, cattle, histopathology, tumor

Introduction

Adrenal gland tumors (AGT) are relatively common. In veterinary medicine, adenomas of the adrenal cortex (ACA) are frequently reported in ferrets (Gliatto et al. 1995, Li et al. 1998), old dogs (Capen 2007) and castrate goats (Altman et al. 1969), but sporadically in other species (Sikora 1953, Vince and Watson 1982). Carcinomas (ACC) occur less frequently, most often in cattle (Wright and Conner

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1968. Edwards and Ralston 2013, Grossi et al. 2013) and old dogs (Chaistain et al. 1978, Vince and Watson 1982, van Sluijs et al. 1995), but rarely in other animals. Among medullary tumors, pheochromocytoma often develops in cattle and dogs, but rarely in other species (Wright and Conner 1968, Froscher and Power 1982, Grossi et al. 2013). Neuroblastomas and ganglioneuromas are also sporadically reported (Capen 2007).

In cattle, AGT have been generally described as single cases (Schofield 1949, Head and West 1955, Monlux et al. 1956, Sandison and Anderson 1968, Wright and Conner 1968, West 1975, Riley and Forsyth 1976, Yarrington and Capen 1981, Hamir 1984, Ladds et al. 1990, Labelle and De Cock 2005, Seimiya et al. 2009, Edwards and Ralston 2013, Grossi et al. 2013). However, they are considered relatively common and usually reported as incidental findings in older animals with rare occurrence of distant metastases or clinical manifestations (Capen 2007, La Perle and Capen 2007), although scarce data are available about their real incidence, pathological characterization, classification criteria and immunohistochemical profile.

In human medicine, ACA are generally single nodules of various size organized in alveoli, cords or nests, resembling the architecture and cytological features of normal adrenal cortex. Nuclear atypia, necrosis, haemorrhages and increased mitotic activity have been rarely and sometimes equivocally reported (Cohen 1966, Lloyd et al. 2002, Lack 2007, Tissier 2010). ACC are rare but carry a grim prognosis because of their propensity to metastasize early (Barlaskar and Hammer 2007). The pathological diagnosis of ACC is challenging for its rarity and the presence of special variants (Volante et al. 2008). The Weiss scoring system, introduced 27 years ago, is still the most widely employed method for assessing malignancy and is based on the recognition at light microscopy of nine morphological parameters, including high-grade features (e.g., nuclear atypia, high mitotic index, atypical mitotic figures and necrosis) and signs of invasion through the tumor capsule or blood vessels (Papotti et al. 2011). However, such morphological features are heterogeneously distributed across individual cases making the distinction between benign and malignant forms sometimes problematic. Immunohistochemistry is generally not of practical value in the routine diagnostic procedure to distinguish benign from malignant adrenocortical tumors but rather to distinguish cortical versus medullary, non epithelial or metastatic tumors.

Among the neoplasms originating from the adrenal medulla, the most frequent are pheochromocytomas, paragangliomas, neuroblastomas and ganglioneuroblastomas.

Because in bovine pathology scarce data are available about the characterization of AGT, aim of the present study was to provide a detailed description of the morphological and immunophenotypical characteristics of a series of bovine AGT in comparison with the human pathology.

Materials and Methods

Between 2004 and 2011, both adrenal glands from 3760 consecutive cattle slaughtered in a slaughterhouse in northern Italy were submitted to careful standard inspection by one of the author (BP) to evaluate the presence of suspicious pathological findings. The cattle included in this study were all females (mean age 5.6 years, range 4-13). Most were Holstein Friesian breed or dairy cattle from various regions of Italy, but the majority (80%) were from the Po Valley.

All glands showing macroscopic lesions were submitted to histopathological examination at the Department of Veterinary Sciences, University of Torino, for a total of 203 samples. Formalin-fixed glands were macroscopically examined; samples of the lesions were paraffin-embedded and routinely processed. Histopathological evaluation was performed on haematoxylin and eosin (H&E) stained sections independently by three observers (MTC, EB and MV); discordant cases were reviewed at a multi-head microscope until a consensus was reached. The following pathological parameters were recorded: type of growth, cellular shape and dimension, cytoplasmic characteristics, mitotic index (MI) (in 10 high power fields – 400 HPF) and presence of nuclear atypia, necrosis, haemorrhage, vascular or capsular invasion, calcifications, and hyaline globules.

Histochemical staining methods included the silver impregnation-based kit (Bio Optica, Milan, Italy) to define the status of the reticulin framework, Grimelius silver stain to assess the neuroendocrine phenotype of the medullary tumors, and the periodic acid-Schiff (PAS) method to better characterize the hyaline inclusions observed in the cortical tumors (see below).

Primary antibodies for immunohistochemistry (IHC) and working conditions are detailed in Table 1. Antigen unmasking was performed in EDTA 0.01 M, pH 9 buffer (for Ki-67, vimentin and pan-cytokeratin) or in citrate buffer 0.01 M, pH6 (for melan-A, chromogranin A, S-100, synaptophysin and neurofilaments) in a water bath at 98°C for 1 hour. Sections were then incubated with 1% hydrogen peroxide in methanol (for 15min at room temperature) and with 5% normal goat serum (for 1h at room temperature) before incubation with the primary antibodies.

Table 1. List of primary antibodies and working conditions.

Antibody	Clone	Dilution	Incubation	Source
Ki-67	mouse anti-MIB-1	1:300	2h at RT	Dako, Glostrup, DK
Melan A	mouse anti human-A103	1:50	2h at RT	Dako, Glostrup, DK
Chromogranin A	mouse anti-LK2H10	1:500	2h at RT	Diagnostic BioSystems, Pleasanton, CA
Synaptophysin	Polyclonal	1:100	2h at RT	Neomarker, Freemont, CA
Vimentin	mouse anti-V9	1:350	2h at RT	Dako, Glostrup, DK
Pan-cytokeratin	pooled – mouse anti AE1/AE3 and mouse anti-CK8 (35BH11)	//	2h at RT	Dako, Glostrup, DK + Cell Marque, Rocklin, CA
Neurofilaments	pooled mouse anti NF68kD, NF160kD and NF 200kD	//	2h at RT	Dako, Glostrup, DK
S-100	Polyclonal	1:2500	2h at RT	Dako, Glostrup, DK

Legend. RT: room temperature

Primary antibody detection was performed using a Dako Real Envision Detection System Peroxidase kit (Dako, Glostrup, Denmark) and "visualized" with diaminobenzidine-tetrahydrochloride (DAB-Sigma-Aldrich, St. Louis, Missouri, USA) followed by H&E counterstaining.

Normal bovine adrenal gland tissue adjacent to the tumour mass was used as control (18 samples). The correlation between the presence of capsule/vascular invasion and other major pathological parameters, including the proliferation index, was tested using contingency Fisher or non-parametric Mann-Whitney tests, as appropriate, run on GraphPad Prism 5.0 software (San Diego, CA, USA).

The comparison with the human tumours was made on the basis of the literature (de Krijger et al. 2012, Papotti et al. 2014, Nakamura et al. 2015) and of the personal experience of one of the author (MV).

Results

Among the 203 glands sequestered by the veterinary inspector because of the presence of suspicious lesions at gross examination, 35 presented microscopically proliferative primary lesions, classified as focal hyperplasia (8/35; 22.8%), primary tumors (27/35 of which 15 involving the cortex and 12 the medulla; 77,2%). Adrenal disease was unilateral in all cases. The non-proliferative lesions in this series, including foci of coagulative necrosis, extra-medullary myelopoiesis and haemorrhages, have been described by our group in a previous study (Biasibetti et al. 2012).

Focal cortical hyperplasia. It presented as single or multiple (1 case, only), well-defined nodules, yellow to grey in color, less than 1 cm in largest size (0.3-0.8 cm), involving the zona glomerulosa of the adrenal cortex or located at the corticomedullary junction. Histologically, focal hyperplasia was well circumscribed and characterized by hypertrophic well-differentiated epithelial cells, with no cellular pleomorphism and a very low MI (1x10 HPF or less).

Primary cortical tumors. Cortical tumors were classified into four patterns based on morphological and immunohistochemical findings (Table 2).

Pattern I (8 cases) were single neoplasms (diameter 1-3.3 cm), white to yellow in color, solid or partially cystic. Histologically, the tumors had a mixed solid, alveolar or papillary architecture with large intercellular spaces; neoplastic cells were large in size and polyhedral or ovoidal in shape with clear to pale eosinophilic cytoplasm (Fig. 1A). Nuclear atypia was variable. Widely, scattered, dense mineral deposits, sometimes forming psammomatous calcifications, were always present. Multifocal interstitial hyaline globules, intensely PAS-positive, were almost always observed. Necrosis and haemorrhage were rare (1 case); vascular or capsular invasion was observed in one half of the cases. The MI was low (1x10 HPF or less) and the Ki-67 proliferation index ranged from 1 to 8%. Melan-A was focally expressed in 2 cases, only. Vimentin expression was present in all cases with a patchy distribution. Pan-cytokeratins were expressed in 7 cases but with a focal distribution in single cells or small cellular aggregates. S100 was heterogeneously expressed in 5 out of 8 tumors. The reticulin network in 6 of these neoplasms was disrupted.

Pattern II (4 cases) was characterized by solid (diameter 0.75-1.5 cm), homogeneous whitish single neoplasms, except for 1 case presenting a multi-cystic appearance. These neoplasms showed cellular features similar to subtype I (including multifocal interstitial

Table 2. Selected criteria to differentiate primary cortical and medullary tumors.

Parameters	Normal tissue		Hyperplasia	Cortical pattern I	Cortical pattern II	Cortical pattern III	Cortical pattern IV	Pheochromocytoma	Neuroblastoma
Number of cases	164		8	8	4	2	1	5	7
Size (mean range: cm)	NP		0.3-0.8	1-3.3	0.75-1.5	0.5-2.1	3.6	2-22	2-3.2
MO Size (mean range: mm)	NP		2-6	5-25	5-20	3-12	>30	9->30	2-25
Architecture	Columns Small groups		Columns Small groups	solid, alveolar or papillary; large intercellular spaces	solid (more), alveolar or papillary; tiny intercellular spaces	micro-nodule separated by thin-loose connective tissue	solid	small lobules branched by connective septa	solid with cellular organization in pseudo-rosettes
Nuclear atypia			absent	present (8/8)	present (4/4)	present (2/2)	present (1/1)	present (5/5)	present (7/7)
Cell/cytoplasm	polyhedral cells		large polyhedral	large, polyhedral or ovoidal; clear to pale eosinophilic	large, polyhedral or ovoidal; clear to pale eosinophilic	large, polyhedral eosinophilic	large polyhedral or spindle-shaped; eosinophilic	large polyhedral or spindle-shaped; eosinophilic; more finely granular and indistinct in cases with malignant features	round to ovalar, scant
Hemorrhages	absent		absent	rare (1/8)	absent	absent	present	present (5/5)	absent
Necrosis	absent		absent	rare (1/8)	absent	absent	present	present (2/5)	absent
Invasion	absent		absent	present (4/8)	present (1/4)	present (1/2)	present	present (2/5)	absent
Calcifications	absent		absent	diffuse multifocal, dense (8/8)	present (3/4)	present (1/2)	absent	present (2/5)	absent
Hyaline globules	absent		absent	present (7/8)	present (4/4)	absent	present	absent	absent
Mitotic index (mean – range)	0-1x10HPF		0-1x10HPF	0-1x10HPF	0-1x10HPF	0-1x10HPF	4x10HPF	1- 29x10HPF	0-1x10HPF
	cortex	**medulla**							
Ki-67 (mean – range)	0.7%	1.5-3.08%	NP	1-8%	2-9%	1-18%	NE	1-72%	2-6%
Pan-cytokeratin	+ (zona glomerulosa)	–	NP	+ (7/8)	+ (3/4)	+ (1/2)	NE	–	-
Vimentin	+	–	NP	+ (8/8)	+ (4/4)	+ (2/2)	+	+ (3/5)	+ (7/7)
Melan A	+	–	NP	+ (2/8)	–	–	–	–	–
S-100	+	–	NP	+ (5/8)	+ (3/4)	+ (2/2)	+	–	NP
Chromogranin A	–	+	NP	–	–	–	–	+ (1/5)	+(7/7)
Synaptophysin	–	+	NP	–	–	–	–	–	+(7/7)
Neurofilaments	–	+	NP	–	–	–	–	–	+ (7/7)
Reticulin	NP	NP	NP	preserved (2/8)	preserved (3/4)	preserved (2/2)	disrupted	NP	NP

Legend. MO Size: mean diameter at light microscopy. NE: not evaluable. NP: not performed

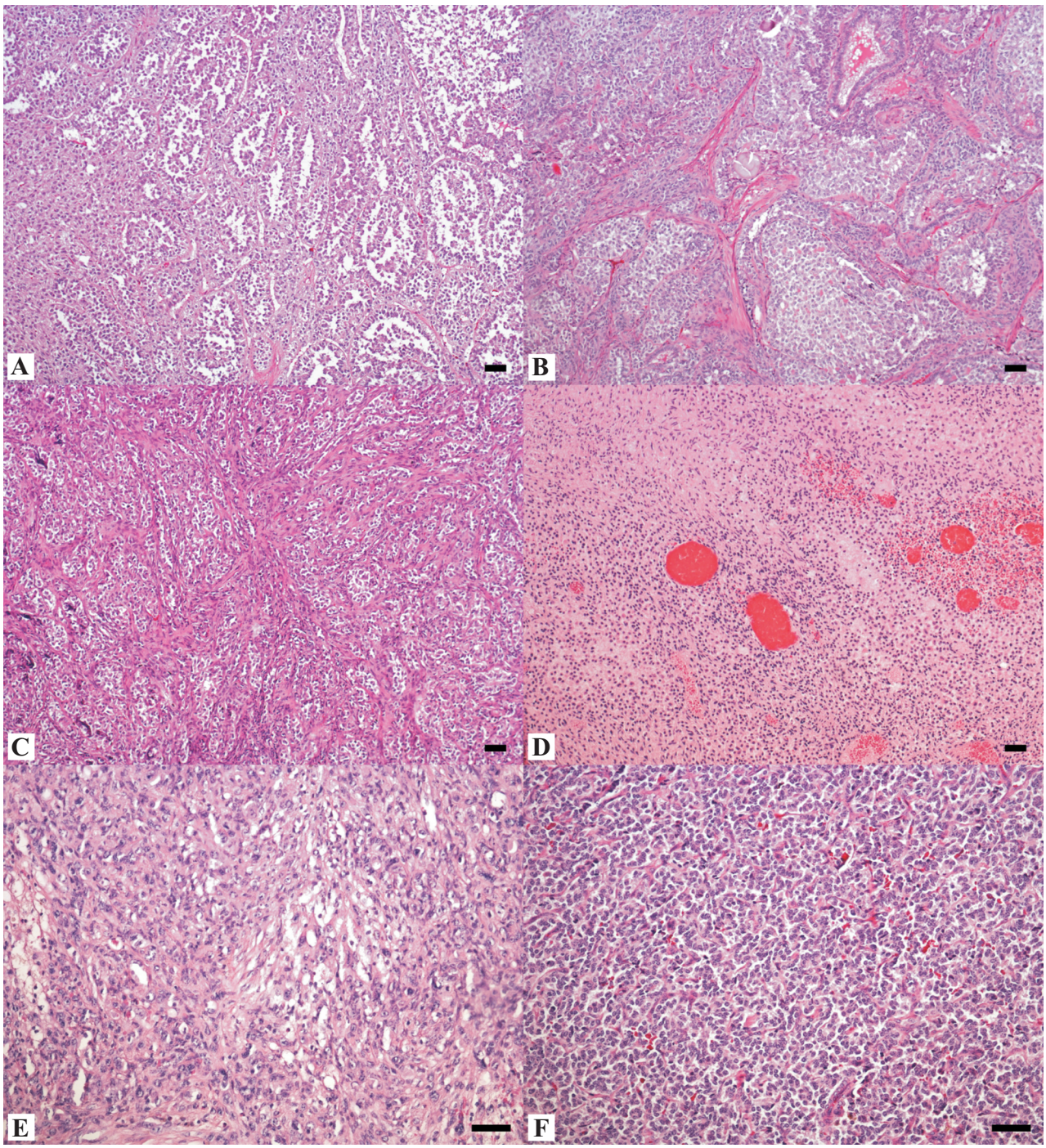

Fig. 1. (A) Cattle, adrenal grand cortical tumor: pattern I. Admixture of solid, alveolar or papillary arrangement with large intercellular spaces. (B) Cattle, adrenal grand cortical tumor: pattern II. Tumor cells organized in a more solid architecture, with papillae or alveoli only occasionally present and tiny intercellular spaces. (C) Cattle, adrenal grand cortical tumor: pattern III. Tumor cells organized in micronodules separated by thin, loose connective tissue. (D) Cattle, adrenal grand cortical tumor: pattern IV. Solid tumor composed of neoplastic cells having a polyhedral or spindle-shaped appearance showing haemorrhages and necrosis. (E) Cattle, adrenal gland medullary tumor, pheochromocytoma. Cuboidal or spindle-shaped neoplastic cells organized in small lobules separated by connective septa. (F) Cattle, adrenal gland medullary tumor, neuroblastoma. Solid neoplasia with cellular organization in pseudorosettes. Haematoxylin and eosin. Bar = 50 μm.

PAS-positive hyaline, 4/4 cases) but solid architecture was predominant (Fig. 1B). Intercellular spaces were tiny, no necrosis was detected, whereas vascular invasion was observed in 1 case. The MI was low (1x10 HPF or less) and the Ki-67 proliferation index ranged from 2 to 9%. The immunohistochemical profile of vimentin and pan-cytokeratins was similar to subtype I. S100 was expressed in 3 out of 4 neoplasms. Three

neoplasms showed a regularly distributed reticulin network.

Pattern III (2 cases) comprised solid, single, micronodular tumors located at the periphery of the gland. Macroscopically, they had a clear and homogenous cut surface and a small size (2.1 cm in largest diameter). Histologically, the tumors were composed of large polyhedral and eosinophilic cells arranged in micronodules separated by loose connective tissue (Fig. 1C). Moderate nuclear atypia and calcifications were detected, whereas necrosis and hyaline globules were absent. One case had capsular invasion. The MI was low (0-1x10 HPF) and the Ki-67 index ranged from 1 to 18%. Pan-cytokeratins were multifocally expressed in 1 tumor, whereas S100 and vimentin were expressed in both tumors; the reticulin network was always preserved.

A single case showed peculiar features unlike any of those reported above and was therefore classified as pattern IV. It was a voluminous, variegated neoplasm (3.6 cm in largest diameter) compressing the adjacent cortical parenchyma and extending into the medulla. Tumor architecture was solid, with polyhedral or mostly spindle-shaped neoplastic cells having abundant eosinophilic cytoplasm (Fig. 1D). Nuclear atypia, haemorrhages, necrosis, PAS-positive hyaline globules, and vascular invasion were present. Calcifications were absent. The MI was 4x10 HPF; the Ki-67 index was not assessable due to altered fixation. Vimentin protein was expressed by the majority of the cells, whereas all other markers were negative except for S100. Disruption of the reticulin network was observed.

Primary medullary tumors. Pheochromocytoma (5 cases). Two of them were voluminous tumors invading nearly the entire gland and the surrounding tissues, with multiple areas of necrosis and haemorrhages suggestive for malignancy. Neoplastic cells were organized in small lobules branched by connective septa. The tumor cells were cuboidal or spindle-shaped, with large hyperchromatic nuclei, and eosinophilic, finely granular, indistinct cytoplasm (Fig. 1E). Calcifications were also present. The other 3 cases were more homogenous (diameter 2-2.97 cm), friable neoplasms, white to yellow in color. They were composed of large polyhedral or spindle-shaped eosinophilic cells. Nuclear atypia and hemorrhages were focally present and no invasion of the peripheral tissues was evident. Lymphoid aggregates were detected at the periphery. The MI was particularly high in 1 case (29 x 10 HPF, Ki 67 index 72%) and low to medium in the others (mitotic index 1-8x10 HPF, Ki-67 index 1-7%,). Vimentin was positive in 3 cases, although focally, whereas chromogranin A was positive in one malignant pheochromocytoma; the neuroendocrine nature of the other ones was determined by positive Grimelius stain.

Neuroblastoma (7 cases).These neoplasms were voluminous (3.2 cm in largest diameter), white in color, well-demarcated, involving the medulla and extending into the adjacent cortex. Typical solid growth with cellular organization in pseudorosettes was observed. Cells were round to ovalar, with hyperchromatic nuclei and scant cytoplasm (Fig. 1F). Nuclear atypia was minimal and necrosis and calcifications were absent. The MI was low (0-1x10 HPF; Ki-67: 2-6%). A diffuse expression of neurofilaments was present in all cases. Focal immunopositivity for vimentin, chromogranin A, and synaptophysin was also detected.

Discussion

The veterinary literature provides a general description of AGT in many species; however, accurate pathological characterization and classification are limited by poorly defined morphological parameters and scarce data on immunohistochemical markers. Furthermore, the distinction between ACA and ACC relies on the recognition at light microscopy level of cellular features, mitotic index, presence of necrosis, haemorrhage and lympho-vascular and/or capsular invasion. Since most of these aspects are also described in cases classified as benign, a detailed description of the specific features that could aid in establishing a diagnosis of malignancy is needed. A recent report by Grossi and coworkers on bovine adrenal gland neoplasms (Grossi et al. 2013) segregated benign and malignant tumors based on the presence of at least three out of five malignancy-related parameters, but a large degree of overlap between the two groups was described. Finally, bovine AGT are assumed to be classifiable as the human counterpart, although a comparative analysis has never been performed. In this scenario, we collected a series of AGT to describe in detail their morphological and phenotypical aspects and to compare their most relevant features with those of the human pathology. Although with the limitations of determining disease incidence from slaughter samples but using an approach similar to other studies in the literature (Wright and Conner 1968, Edwards and Ralston 2013, Grossi et al. 2013), we found proliferative lesions in 0.93% of adrenal glands in our series. Wright and Conner (1968) reported hyperplastic nodules in 31 out of 26,667 cattle (0.11%) in both the cortex and medulla. Even excluding hyperplastic nodules, the incidence of AGT in our series remained very high (0.72%). Primary tumors (77.2%, incidence 0.72%) and, among those, cortical neoplasms (0.40%)

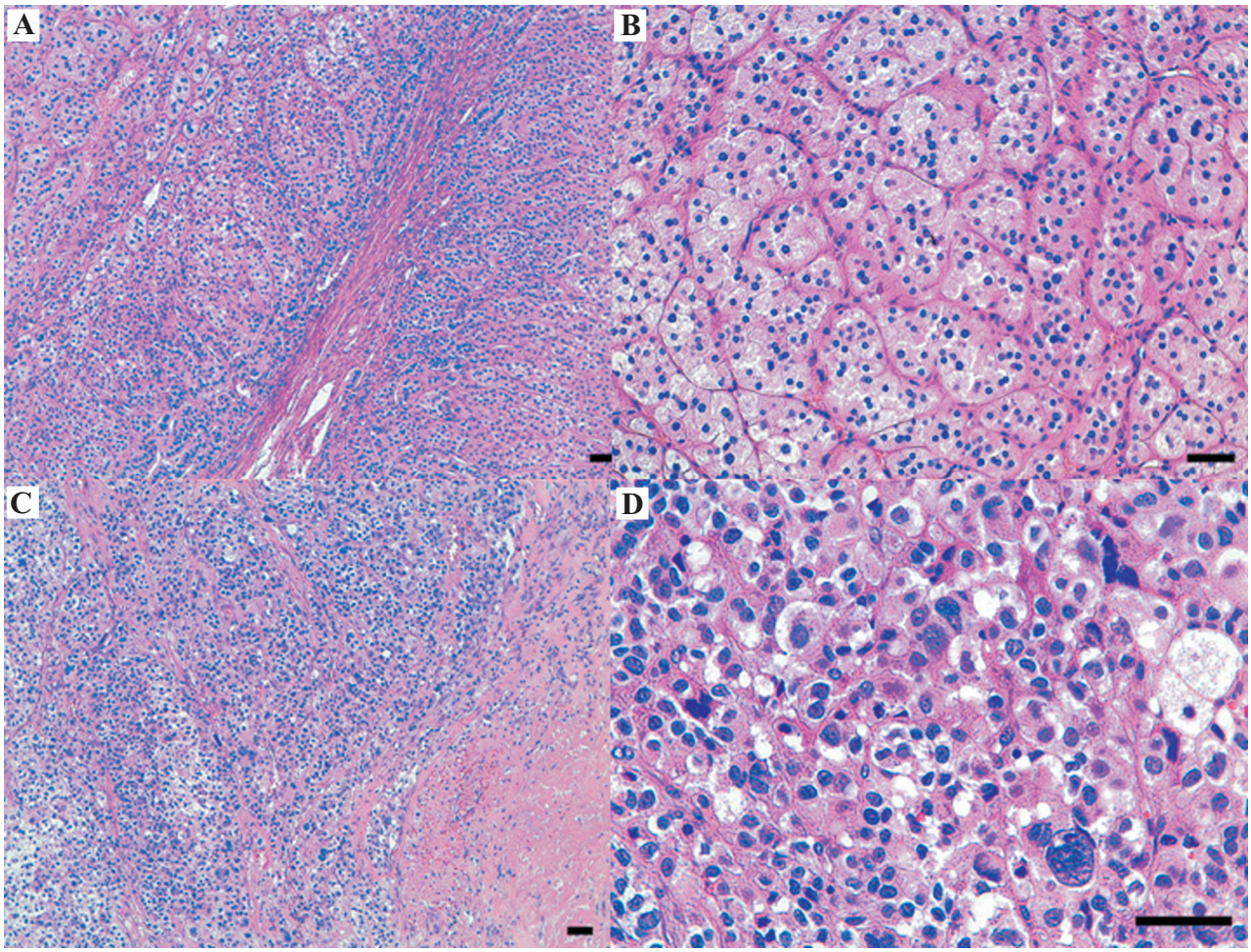

Fig. 2. (A) Human, adrenocortical adenoma showing typical alveolar architecture (left) similar to adjacent normal adrenal (right). (B) Human, adrenocortical adenoma. Clear cells with large foamy cytoplasm and small typical nuclei without nucleoli. (C) Human, adrenocortical carcinoma with necrosis and diffuse growth pattern. (D) Human, adrenocortical carcinoma composed of tumor cells with eosinophilic cytoplasm, severe nuclear pleomorphism and mitotic figures. Haematoxylin and eosin. Bar = 50 μm.

were most frequent, in line with the available literature (Wright and Conner 1968, Capen 2007, Edwards and Ralston 2013, Grossi et al. 2013). As in other similar studies, functional activity and endocrinological conditions were not evaluable in our bovine series in the absence of clinical information. The multiple endocrine syndrome described in bulls (Wilkie and Krook 1970, Black et al. 1973, Sponenberg and Entee 1983, Seimiya et al. 2009) was not assessable because all the examined animals were female. As to concern morphological aspects, the group of cortical tumors as a whole showed a very heterogeneous spectrum of patterns that do not fit into the two major diagnostic categories of adenoma and carcinoma, in either cattle or humans (Fig. 2). Malignancy-related parameters were variably present in the different cortical types, suggesting that each specific pattern is not associated with a unique biological behavior. Therefore, the different patterns of cortical tumors herein proposed are intended exclusively for descriptive purposes. In both the veterinary and human literature, adenomas may show areas of necrosis, cysts, calcifications, and haemorrhages (Cohen 1966, Wright and Conner 1968, Lloyd et al. 2002, Capen 2007, Lack 2007, Tissier 2010). These features were also commonly detected in our series, particularly in patterns I and II. A specific feature shared by cortical tumor patterns I, II, and IV was the presence of interstitial hyaline globules, which are also reported in human medicine in pheochromocytomas and in an oncocytic tumours (Al-Zaid et al. 2008). Al Zaid and coworkers (2008) hypothesized that these accumulations may be related to lipid storing associated with the presence of adipose differentiation-related protein (Ducharme and Bickel 2008). The role of these protein accumulations in bovine AGT remains to be elucidated. The immunohistochemical profile of cortical lesions was heterogeneous across the different patterns and different

Table 3. Association between pathological parameters and the presence of vascular and/or capsular invasion in primary cortical and medullary tumors.

	Mean size (mm) [range]	Presence of necrosis	Mitotic index >1	Mean mitotic index [range]	Mean Ki-67 index [range]	Disruption of the reticulin framework
Invasion absent (#11)	10.1 [3-20]	0/11	1/11	1.6 [1-8]	3.1 [1-9]	6/10*
Invasion present (#9)	22.4 [12-30]	4/9	3/9	4.4 [1-29]	16 [2-72]	4/6*
	Mann Whitney test: **p<0.001**	*Fisher test:* **p=0.026**	*Fisher test:* p=0.28	*Mann Whitney test:* p=0.23	*Mann Whitney test:* **p=0.019**	*Fisher test:* p=1.0

Legend: * – reticulin staining not assessable in 4 cases.

from the immunohistochemical profile of human cortical neoplasms. In humans, adrenocortical tumors, irrespective of their benign or malignant nature, express alpha-inhibin and melan-A; they are usually negative or only focally positive for cytokeratins, and are invariably positive for vimentin. Positivity for neuroendocrine markers is restricted to synaptophysin, whereas chromogranin A is always negative, a feature that helps in the differential diagnosis with pheochromocytoma (Cohen 1966, Lack 2007, Volante et al. 2008, Tissier 2010). In our series, the most reliable markers of cortical origin were vimentin and S-100, whereas melan-A was only occasionally and focally expressed. The second most prevalent tumor type was represented by seven cases of neuroblastoma, with an incidence of 0.19%, higher than the 0.03% reported in the literature (Wright and Conner 1968), whose morphological and immunophenoptypical features largely overlapped with those of the human counterpart. Pheochromocytoma incidence was similar to previous studies (0.13% in our series vs. 0.17% in Wright and Conner 1968). Two cases were morphologically classified as malignant, although metastatic disease was not demonstrated, and a third case showed the presence of invasion. Differently from the human pathology, spindle-shaped cells predominated in most cases and the specific immunophenotype was not significantly different from the human counterpart, except for chromogranin A which was not as sensitive as in the human pathology. In the present study, the lack of evidence of metastases in any of the tumors precluded making a definitive "clinical" distinction between benign and malignant tumors of either the cortical or medullary type. In addition, and similarly to Wright and Conner (1968), no gross evidence of metastatic lesions was reported by the veterinary inspector even though the major organs (e.g., lungs, liver, spleen, and kidneys) were sectioned several times. Invasion of the vena cava was never reported, at variance with a recent survey by Edwards and Ralston (2013). However, assuming that the presence of either capsular or vascular invasion represents the most reliable morphological parameter of biological malignancy also in veterinary medicine (Monlux et al. 1956, Misdorp 1967, Wright and Conner 1968, Hamir 1984, Gil 2005, Edwards and Ralston 2013, Grossi et al. 2013), we compared the presence of invasion with other relevant pathological parameters (Table 3). We noted that the cases with morphological signs of invasion were significantly associated with large size, higher proliferation index, presence of necrosis and – with a trend towards significance – higher mitotic index, but not with several other morphological criteria (e.g., cell pleomorphism, growth pattern, and spindle-cell morphology) suggested by Grossi et al. (2013). Moreover, at variance with the human pathology (Volante et al. 2009), disruption of the reticulin scaffold was not a reliable marker of malignancy. Diagnostic issues aside, the importance of distinguishing between benign and malignant tumors is quite different in human and bovine pathology. In animal species regularly slaughtered for human consumption, the interest in tumor pathology is limited to the identification of localized neoplasms or metastatic tumors for their exclusion from consumption (Regulation EC 854/2004) and justifies the few studies in this area.

Conclusion

In summary, this paper gives a detailed description of the morphological and phenotypical aspects of a series of bovine AGT and compares the features most relevant to the human pathology. Although limited by the small number of neoplasms and the lack of identification of metastatic lesions, this study represents the first attempt to compare the bovine and human pathology in terms of its morphological and immunophenotypical characteristics. Our data support the concept that adrenal tumors in cattle have distinctive features that deserve a species-specific classification.

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