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# Malignant epithelioid mesothelioma in senile Red Sindhi cows from Brazil[1]

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**ABSTRACT.-** Oliveira M.C., Miranda I., Daoualibi Y., Lopes S.P., Pereira A.H.B., Souza B.G., Negrão Watanabe T.T., Armién A.G., Ubiali D.G. & Brito M.F. 2023. **Malignant epithelioid mesothelioma in a senile Red Sindhi cows from Brazil.** *Pesquisa Veterinária Brasileira 43:00, 2023.* Setor de Anatomia Patológica, Instituto de Veterinária, Universidade Federal Rural do Rio de Janeiro, BR-465 Km 7, Seropédica, RJ 23890-000, Brazil. E-mail: danielubiali@ufrrj.br

Mesotheliomas in cattle are often described as isolated case reports, and investigations of multiple cases within the same bovine herd are lacking. A series of cases of malignant epithelial mesothelioma, tubulopapilary type, is described in five 15 to 21-year-old Red Sindhi cows from the same herd. Clinical signs included three to eight months of progressive emaciation, dehydration, subcutaneous edema of the lower extremities, and abdominal distension. Grossly, severe subcutaneous edema and hydroperitoneum were noted. Multiple organs' parietal and visceral serosal surfaces had multifocal to coalescing yellow, firm, sessile nodules ranging from 0.1 to 29.0cm. Similar free nodules floated in the peritoneal fluid. Histologically, the masses comprised a layer of cubic to columnar neoplastic cells forming papillary or cystic proliferation supported by a dense fibrovascular stroma. Neoplastic cells had strong and diffuse cytoplasmic immunolabeling for pan-cytokeratin but were negative for cytokeratin 7 and vimentin. Ultrastructurally, neoplastic cells had delicate microvilli and tight and anchoring junctions. Within the cytoplasm, a moderate amount of loose aggregate of intermediary filament with small mitochondria was observed. Epidemiological investigation evidenced endogamy in this herd. Asbestos exposure was not detected. The diagnosis was based on clinical, gross, histological, and immunohistochemical findings and confirmed by transmission electron microscopy features. A definitive underlying etiology remains unknown.

INDEX TERMS: Bovine, veterinary pathology, cytokeratin, immunohistochemistry, transmission electron microscopy.

**RESUMO.-** [**Mesotelioma epitelial maligno em vacas senis Sindi do Brasil.**] Mesotelioma em bovinos são frequentemente relatados como casos isolados, descrições de múltiplos casos no mesmo rebanho bovino não foram encontrados. Descreve-se uma série de casos de mesotelioma epitelial maligno, tipo tubulopapilar, em cinco vacas Red Sindi de 15 a 21 anos de idade do mesmo rebanho. Os sinais clínicos incluíram emagrecimento progressivo, desidratação, edema subcutâneo das extremidades dos membros e distensão abdominal em um curso clínico que variou de três a oito meses. Macroscopicamente, observou-se edema subcutâneo acentuado e hidroperitônio. Nas serosas parietais e viscerais de múltiplos órgãos haviam nódulos multifocais a coalescentes amarelo-claros, firmes e sésseis que variavam de 0,1 a

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29,0 centímetros de diâmetro. Nódulos livres semelhantes também flutuavam no líquido peritoneal. Histologicamente, as massas eram compostas por uma camada de células cúbicas a colunares formando proliferação papilar ou cística sustentada por estroma fibrovascular denso. As células neoplásicas apresentavam imunomarcação citoplasmática forte e difusa para pan-citoqueratina, mas eram negativas para citoqueratina 7 e vimentina. Ultraestruturalmente, as células neoplásicas apresentavam delicadas microvilosidades e junções comunicantes e de ancoragem. No citoplasma observou-se moderada quantidade de agregados de filamentos intermediários soltos e pequenas mitocôndrias. A investigação epidemiológica revelou que não houve inserção de bovinos de outros rebanhos por mais de 30 anos e evidenciou endogamia. Não foram encontradas possíveis fontes de amianto para os bovinos deste rebanho. O diagnóstico de mesotelioma foi baseado em características clínicas, macroscópicas, histológicas, imuno-histoquímicas e confirmado pelos achados de microscopia eletrônica. A etiologia permanece desconhecida.

TERMOS DE INDEXAÇÃO: Bovinos, patologia veterinária, citoqueratina, imuno-histoquímica, microscopia eletrônica de transmissão.

## INTRODUCTION

Mesothelioma is usually a malignant, rare neoplasm arising from mesoderm-derived mesothelial cells of the serosal surface of the thorax, abdomen, or pericardial sac (Schulman 2003). In cattle, mesothelioma occurs more frequently in the abdominal cavity than in the thorax (Hashimoto et al. 1989, Girard & Cécyre 1995). The World Health Organization classified the mesothelioma of domestic animals into three forms with distinct morphology: epithelioid, sarcomatoid, and biphasic (mesenchymal and epithelioid) (Schulman 2003). Diagnosing mesothelioma requires a combination of clinical, gross, histopathological, immunohistochemistry, and, ideally, ultrastructural features (Hashimoto et al. 1989, Hammar 2006). Exposure to asbestos dust has been associated with mesothelioma in humans (Hashimoto et al. 1989) and cattle (Stöber et al. 1990). An old age presentation and a congenital form of mesothelioma are reported in cattle (Schulman 2003). We described a series of cases of malignant mesothelioma in five senile cows from the same herd.

## MATERIALS AND METHODS

From 2014 to 2020, the veterinary pathology team from the "Setor de Anatomia Patológica" (SAP) visited the patrimonial bovine Red Sindhi herd from "Universidade Federal Rural do Rio de Janeiro" (UFRuralRJ) for clinical assistance and environmental inspection. The responsible veterinarian provided epidemiologic data. One cow died, and four were euthanized according to the law regarding the use of animals for scientific purposes from the Ethics Committees for Animal Use (CEUA) in research institutions and the National Council for Animal Experimentation Control. *Postmortem* examinations were performed, and a full set of tissues was collected from all five cows (free masses from the peritoneal cavity, brain, lymph nodes, thyroid, adrenal glands, ovaries, as well as samples of omentum, mesentery, pre-stomachs, abomasum, gall bladder, uterus, intestines, spleen, liver, kidney, lungs, and heart) and submitted to the SAP/UFRuralRJ.

Formalin-fixed tissues were routinely processed for histopathology and stained with hematoxylin and eosin (HE). Selected tissues were stained with Masson's Trichrome, periodic acid-Schiff (PAS), and combined Alcian blue (AB)-PAS.

Immunohistochemistry (IHC) for pan-cytokeratin (Dako®, Clone AE1/AE3, dilution at 1:80), cytokeratin (Dako®, Clone 7, dilution at 1:100), and vimentin (Clone V9, Zimed®, dilution at 1:200) was performed on the neoplasms from four cows using a polymer method (MACH 4, Universal HRP-Polymer, Biocare Medical). For positive control, a canine-haired skin section was used. For negative controls, phosphate-saline buffer (PBS) replaced the primary antibody. For antigenic recovery, pH 6.0 citrate buffer was used for three minutes at 125°C in a digital pressure cooker. The chromogen was 3-Amino-9-ethyl carbazole (AEC, Dako®), and counterstaining was performed with Mayer's hematoxylin.

Additionally, small fragments of the masses were fixed in 2.5% glutaraldehyde in 0.1M cacodylate buffer pH 7.4 (Electron Microscopy Sciences, Hatfield/PA, USA) for ultrastructural examination at the Ultrastructural Pathology Unit at the Minnesota Veterinary Diagnostic Laboratory, USA. The tissue blocks were post-fixed in 1% osmium tetroxide buffered in 0.166M sodium cacodylate (pH 7.4). After three washes in distilled water, samples were dehydrated using a 25%-100% ethyl alcohol gradient. Samples were then infiltrated in EMbed 812 resin (Electron Microscopy Sciences, Hatfield/PA, USA), further embedded, and incubated at 58°C for 24 hours to polymerize the resin. Embedded samples were sectioned on a Leica UC6 ultramicrotome (Leica Microsystems, Vienna, Austria). Thin sections (70-90nm) were contrasted with 5% uranyl acetate for 20 minutes and Santos' lead citrate for 6 minutes. These samples were visualized using a JEOL 1400 transmission electron microscope (JEOL LTD, Tokyo, Japan). Images were obtained using an AMT Capture Engine Version 7.00 camera and software (Advanced Microscopy Techniques Corp. Woburn/MA, USA).

## RESULTS

During the 7-year study, five 15- to 21-year-old cows from a herd with thirty adult cows, five calves, and a bull had a three- to eight-month history of clinical signs. The clinical picture was progressive emaciation, anorexia, dehydration, weakness, severe abdominal distension (Fig.1), and subcutaneous edema in the chest, abdomen, and caudal thigh regions (Fig.2). Epidemiological data revealed endogamy since the herd was established in the '90s decade. For more than 30 years, no bovine from external herds was inserted, and reproductive control was absent for an extended period. During the environmental inspection of the paddocks and corral, there was no evidence of asbestos exposure. The *postmortem* examination showed a poor body condition score and marked abdominal and subcutaneous edema.

Grossly, four cows presented peritoneal masses, and one cow presented concomitantly pleural and peritoneal masses. In all cases, the peritoneal cavity had a large amount of light yellow fluid (80 to 200L). Three cows had 30 to 50L of similar fluid within the pleural cavity. Multiple yellow, large, irregular-to-ovoid, and soft masses were found loose in the peritoneal cavity (Fig.3), or adhered to omentum, and mesenteric tissue. The hepatic capsule over the falciform ligament had multifocal to coalescing, linear, yellow aggregates (Fig.4). Masses of approximately 0.1-29.0cm in diameter were firmly attached and infiltrated in the parietal and visceral peritoneal surface of multiple organs. These nodules occasionally formed vesicles filled with clear liquid or were pedunculated and attached to the mesothelium by small stalks (Fig.5-6). The superficial and mesenteric lymph nodes were enlarged, swollen, and draining clear liquid on the cut. Two cows with severely enhanced intra-abdominal pressure due to ascites had renal lobular fusion and firm dark yellow perirenal fat. Internal examination of the uterus and ovaries revealed normal anatomy. The pleural (parietal and pulmonary) masses were located mainly in the intercostal muscle areas (Fig.7). Table 1 shows detailed gross from the five cows with epithelioid mesothelioma.

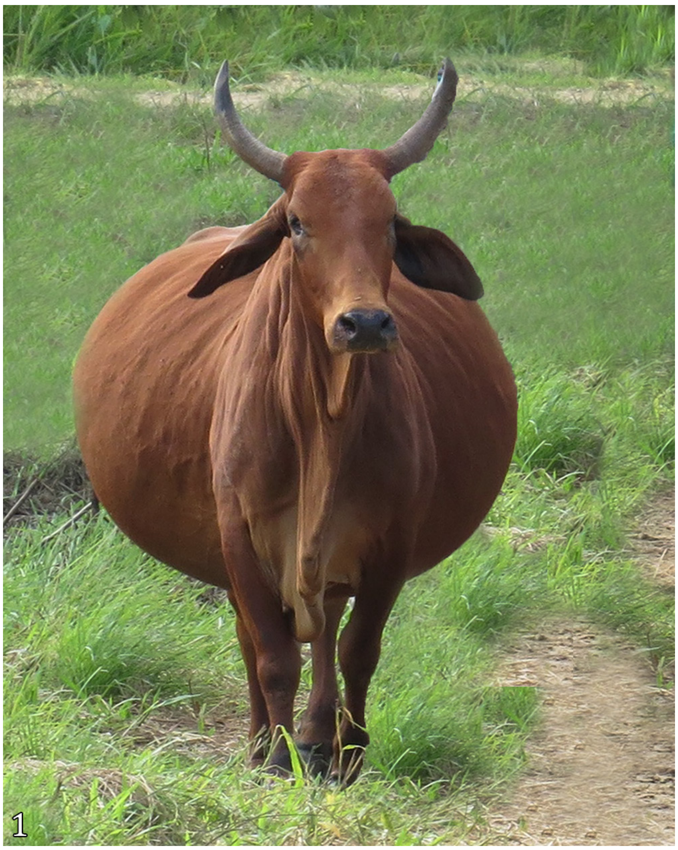


Fig.1. Malignant epithelioid mesothelioma; cow No. 1. Severe and diffuse increase in abdominal volume and severe eyeball retraction inside the orbit due to dehydration.

Histologically, all the masses comprised small to extensive papillary proliferation, sometimes forming cysts (Fig.8-9). A dense fibrovascular stroma supported a single-cell layer of cuboidal to columnar cells. Neoplastic cells had a 2:1 cytoplasm nucleus ratio. The nuclei were small, oval to round, with finely stippled chromatin and one to three nucleoli. Mitotic figures were 2 in 10hpf (2.37mm$^2$). The masses in the omentum and mesentery had epithelioid cells interspersed with adipose tissue with multiple areas of fat necrosis and collagenous tissue deposition. Foci of infiltration across the parietal and visceral peritoneum and organ capsules were identified, and metastatic foci were observed in mediastinal lymph nodes (Fig.10), adrenal, and thyroid. Low numbers of lymphocytes and rare plasma cells mixed with edema were seen within the neoplasm.

The Masson's Trichrome stain highlighted the collagenous stroma and desmoplastic reaction within the neoplasm (Fig.11). The PAS highlighted only the basement membrane of the epithelioid mesothelial neoplastic tissue. The AB-PAS stain


Fig.2. Malignant epithelioid mesothelioma; cow No. 2. Low body score and increased volume in the chest, abdomen and posterior thigh regions due to edema.

**Table 1. Gross findings of malignant epithelioid mesothelioma in five senile Red Sindhi cows**

| | Cow 1 | Cow 2 | Cow 3 | Cow 4 | Cow 5 |
|---|---|---|---|---|---|
| Hydroperitoneum | +++ | ++ | ++ | +++ | +++ |
| Subcutaneous edema | + | ++ | +++ | +++ | + |
| Hydrothorax | ++ | ++ | - | - | +++ |
| Parietal peritoneum neoplastic masses | +++ | +++ | +++ | +++ | ++ |
| Pleural location of neoplastic masses | | | | | |
| Parietal pleura | - | - | - | - | +++ |
| Pulmonary pleura | - | - | - | - | +++ |
| Serosal location of visceral neoplastic masses | | | | | |
| Pre-stomaches and abomasum, omentum, and mesentery | +++ | +++ | +++ | +++ | +++ |
| Liver | ++ | ++ | +++ | +++ | ++ |
| Spleen | ++ | + | +++ | + | ++ |
| Small and large intestines | + | + | +++ | + | ++ |
| Uterus (perimetrium) | ++ | - | - | - | + |
| Urinary bladder | - | ++ | - | + | + |

- Absent, + mild, ++ moderate, +++ severe.

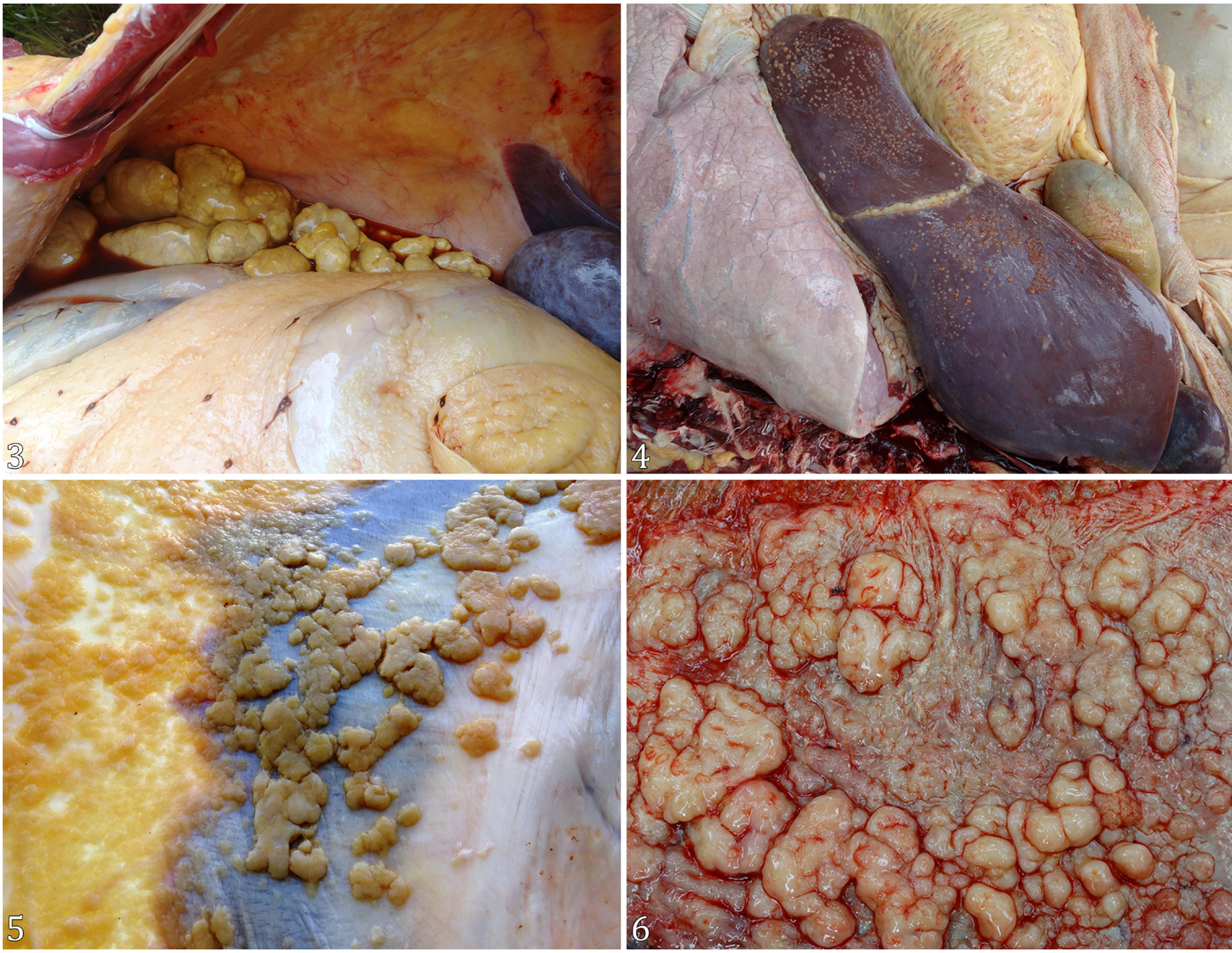


Fig.3-6. Malignant epithelioid mesothelioma; cow No. 3. (**3**) Multiple large yellow irregular to ovoid masses free within the peritoneal cavity. (**4**) Multifocal and cystic masses at the hepatic capsule and multifocal to coalescent yellow masses over the falciform ligament. (**5**) Diaphragmatic peritoneal surface with multiple multifocal to coalescent yellow masses of varying sizes. (**6**) Spleen surface with multiple multifocal to coalescent yellow masses of varying sizes.

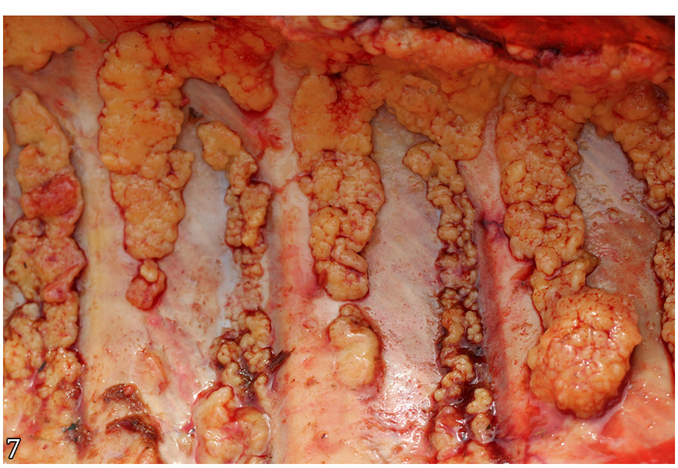


Fig.7. Malignant epithelioid mesothelioma; cow No. 5. Multiple large yellow irregular-to-ovoid multifocal to coalescent masses at the parietal pleural surface, mainly at the intercostal areas.

failed to reveal any intracytoplasmic mucopolysaccharides. Neoplastic cells had strong cytoplasmic immunolabeling for pan-cytokeratin (Fig.12) and were negative for vimentin (Fig.13) and cytokeratin 7.

On ultrathin preparation, neoplastic cells were cuboidal with delicate microvilli and tight and anchoring junctions. Within the cytoplasm was a moderate to a large amount of loose aggregate of intermediary filament, sometimes forming whirls giving the cells a rhabdoid appearance. There were small mitochondria, short rough endoplasmic reticulum cisterns, and sparse polyribosomes and glycogen aggregates. Neoplastic cells presented a round nucleus with marginal heterochromatin and compact nucleolus (Fig.14-16).

## DISCUSSION AND CONCLUSION

Combined gross, histological, histochemical, immunohistochemical, and ultrastructural features were necessary to diagnose this

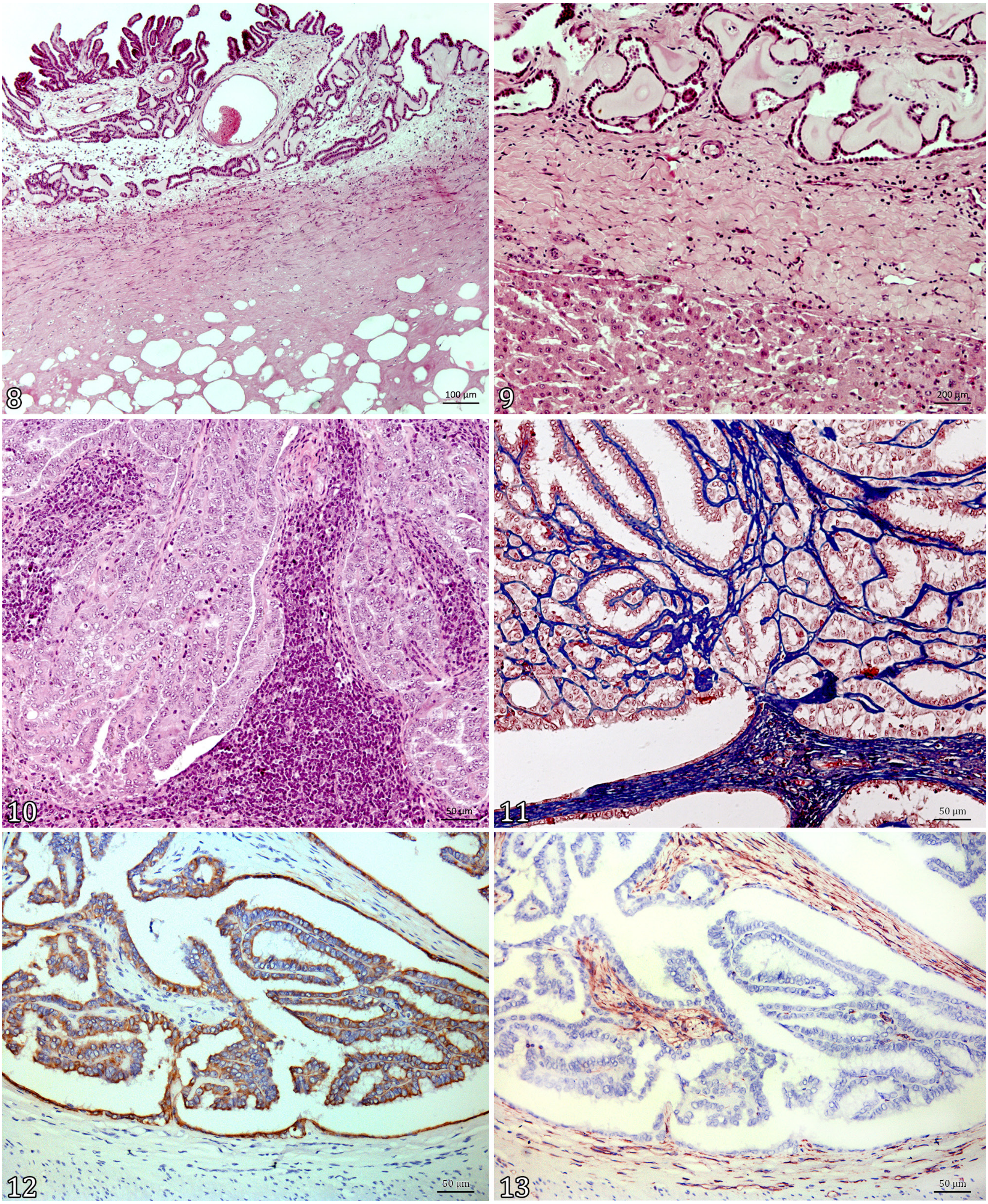


Fig.8-13. Malignant epithelioid mesothelioma; cow No. 3. (**8**) Omentum with a proliferation of a single cell layer of cuboidal to columnar cells forming papillae and cysts supported by a dense fibrovascular stroma. HE, bar = 100µm. (**9**) Cuboidal mesothelial cells from the hepatic capsule are supported by a collagenous stroma. HE, bar = 200µm. (**10**) Lymphatic metastasis was detected by papillary projections of mesothelial cells in the cortical region of lymph nodes. HE, bar = 50µm. (**11**) Collagenous stroma of the neoplasm in the diaphragmatic peritoneum. Masson's Trichrome, bar = 50µm. (**12**) Robust cytoplasmic immunoreactivity of neoplastic cells with pan-cytokeratin (AE1/AE3) antibodies in the ruminal serosa. IHC, bar = 50µm. (**13**) Negative neoplastic cells and positive stromal immunostaining with anti-vimentin antibody in the ruminal serosa. IHC, bar = 50µm.

series of cases of epithelioid mesothelioma in Red Sindhi cows from Rio de Janeiro, Brazil. The low frequency of reported cases of mesotheliomas in cattle reflects the rarity of this tumor in this species (Lucena et al. 2011, Carvalho et al. 2014, Tessele & Barros 2016, Reis et al. 2017). The malignant mesothelioma distinction from carcinoma is sometimes difficult to be made. Similar to humans and various species of domestic animals, the association of gross and histological features is essential for the accurate diagnosis of neoplasms of mesothelial origin (Hammar 2006).

The mesothelial origin of this peritoneal neoplasia in Red Sindhi cattle was previously confirmed by the expression of a cocktail of cytokeratin peptide (cytokeratin 4, 5, 6, 8, 10, 13, 18), by the presence of delicate apical microvilli, tight and anchoring junctions on cuboidal cells observed at the transmission electron microscope (Dardick et al. 1987, Hashimoto et al. 1989, Barak et al. 2004, Mutsaers 2004, Kushitani et al. 2007). However, the lack of reports describing the ultrastructural features for all mesothelioma types in various animal species precludes comparisons. In a case of malignant mesothelioma in a horse, the definitive diagnosis was achieved by evaluating the ultrastructural features of this neoplasm (Schappa et al. 2017). In contrast to the current case, mesothelial neoplastic cells presented long microvilli at basolateral cell surfaces with extracellular neolumina and intracellular vesicles, robust desmosomes, and tonofilaments (Schappa et al. 2017).

The gross hallmark feature in the five cows from this study was the visceral and parietal abdominal serosa with transudate. From five cows, all presented peritoneal epithelioid mesothelioma, and one showed concomitantly pleural epithelioid mesothelioma. Although mesotheliomas' preferential anatomic location in cattle is the abdominal cavity (Braun et al. 2012, Munday et al. 2016), and as in dogs and cats (Munday et al. 2016), this neoplasia has also been reported in the pleura (Beytut et al. 2002, Tharwat et al. 2012), pericardium (Takasu et al. 2006), and tunica vaginalis (Sutton 1988). In contrast, mesotheliomas in humans commonly affect the thoracic cavity (Misdorp 2002). In our case series, metastatic foci were observed in mediastinal lymph nodes, the adrenal gland, and the thyroid gland. In addition, hematogenous and lymphatic metastasis can occur to direct extension metastasis common in mesotheliomas (Cullen & Breen 2017, Munday et al. 2016). Differentiating malignant mesothelioma from metastatic tumors of ovaries and uterus is essential, given that metastatic neoplasms can often cover the external surface of multiple abdominal organs (Munday et al. 2016). Mucin deposits are commonly seen in adenocarcinomas. However, some epithelioid mesotheliomas can be demonstrated PAS- (Girard & Cecyre 1995) and AB-positive cytoplasmic material (Husain et al. 2009). The glandular epithelium and urothelial carcinoma can be ruled out with the help of cytokeratin 7 immunohistochemistry (Barak et al. 2004). Further, gross

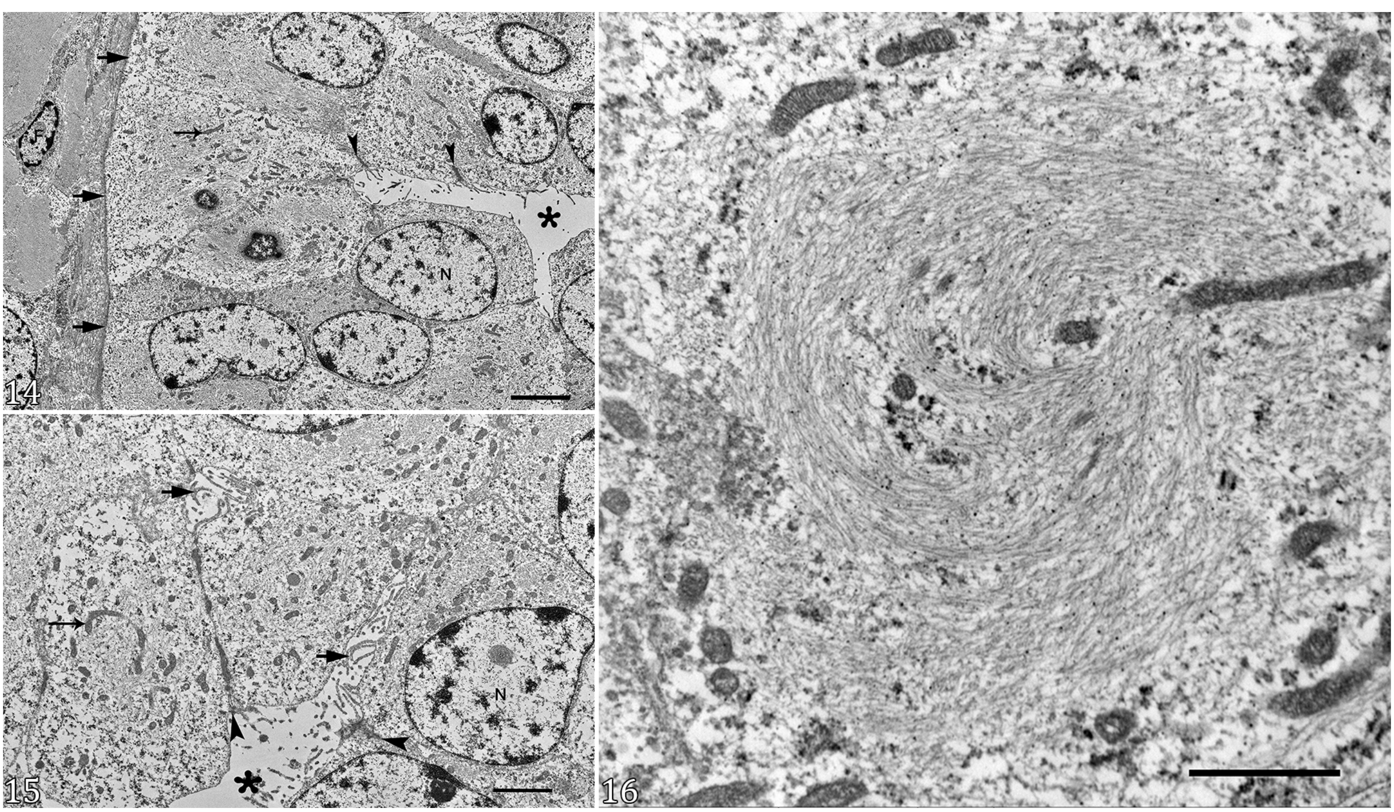


Fig.14-16. Malignant epithelioid mesothelioma. Uranyl acetate/lead citrate ultraphotomicrography of malignant epitheliod mesothelioma; reticulum; cow No 4. (**14**) Neoplastic cells forming a tubule. The basement membrane is signed by arrows, tight junctions are highlighted by arrowheads, the mitochondrion is marked with a small arrow, and the lumen of the tubules is marked by a star; N = nucleus. Bar = 2μm. (**15**) Neoplastic cuboidal cells are projecting delicate microvilli (arrow) into the lumen of a tubule (star), tight junctions are signed by arrowheads, and mitochondrion is marked with a small arrow; N = nucleus. Bar = 2μm. (**16**) Cytoplasm of a neoplastic cell showing a large amount of intermediary filament forming whirls entrapping mitochondria. Bar = 1μm.

differential diagnosis with malignant mesothelioma includes cavitary tuberculoid granulomas due to *Mycobacterium bovis* infection, which can be ruled out with a histological pattern of the inflammatory lesion and acid-fast stain on formalin-fixed paraffin-embedded sections (Domingo et al. 2014).

The etiopathogenesis of mesothelioma in cattle has yet to be elucidated completely. Experimentally, intraperitoneal inoculation of minerals induced mesothelioma formation in rats (Soffritti et al. 2004), similar to asbestos-associated mesothelioma (Robinson et al. 2015). The association between asbestos exposure and pleural and peritoneal mesothelioma in humans is well-documented (Mensi et al. 2011). The asbestos fibers can circulate from the sanguineous circulatory system and reach the peritoneal cavity (Miserocchi et al. 2008). Eight cases of mesotheliomas in adult cattle in Germany originated from farms with a history of using asbestos fibers (Stöber et al. 1990). In the current case, field investigation demonstrated no evidence of asbestos exposure in the facilities or pastures.

Mesothelioma of a spontaneous or familial nature in humans and animals has been reported (Ilgren & Wagner 1991). In the current report, mesothelioma occurred in senile cows born in the same herd and location. In cattle, familial cases are not documented, but the hereditary origin was suggested in calves with mesothelioma (Misdorp 2002, Takasu et al. 2006). Endogamy in this Red Sindhi herd demonstrated a potential hereditary source once the history report states that the successive generations of bulls were from the same bloodline and the bulls crossed with their daughters. Molecular genetic analysis in humans detected mutations in suppressor genes, including cyclin-dependent kinase inhibitor 2A and type 2 neurofibromatosis (NF2) gene (Sekido 2013). In addition, mutations in the germline of the enzyme BAP-1 (Testa et al. 2011), the release of cytokines and growth factors resulting in chronic inflammation (Yang et al. 2010, Butnor et al. 2017), and radiation represent a risk for neoplastic transformation (Goodman et al. 2009). Thus, we recommend a further molecular genetic investigation to detect potential gene mutations involved in the hereditary origin of Red Sindhi cows' mesothelioma.

An underlying etiology for the neoplasms in these cows remains uncertain but suggested hypotheses include carcinogens of prolonged action or a hereditary origin with late manifestation.

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