

METASTASIZING OVARIAN CARCINOMA IN AN EURASIAN BROWN BEAR (*Ursus arctos arctos*): A CASE REPORT

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Summary: A case of ovarian carcinoma, never previously reported in bear is described. A 37-year-old, nulliparous, female Eurasian brown bear hosted at the Falconara Parco Zoo in Italy, showed neurological clinical signs including bilateral blindness and signs of hemiparesis involving both limbs of the left side.

A therapy based on fluid, dexamethasone sodium phosphate, ranitidine, ceftriaxone, propentofylline, and a vitamin B complex administration was started after the onset of symptoms. After about a week of therapy the bear was able to stand up and walk, partially recovered the vision and ate regularly. Despite this initial improvement, three weeks after the clinical onset the bear died. At necropsy a large tumourous mass involving the left ovary and spread of tumour metastases to the regional lymph node and brain has been found. Based on the typical histological and immunohistochemical features of neoplastic cells, this tumor was diagnosed as papillary to solid serous type ovarian carcinoma. Because of the scattered distribution pattern of neoplastic nodules, the involvement of the brain and lumbo-aortic lymph node was considered to be metastatic. Only few reports of neoplasms in Ursidae can be found in scientific literature and these include lymphosarcoma, osteoma, osteosarcomas, chondrosarcoma, squamous cell, biliary, thyroid, mammary, and hepatocellular carcinomas. According to these results, the presence of tumor should be considered in bears with neurological signs.

Keywords: brain; brown bear; metastases; ovary; tumor

Case description

Only few reports of neoplasms in *Ursidae* can be found in scientific literature (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14) and none of this refer about ovarian tumor.

A 37-year-old nulliparous female Eurasian brown bear (*Ursus arctos arctos*) 87 Kg in weight, hosted at the Falconara Parco Zoo, in Italy, was referred because found in lateral recumbency.

The bear was borne in the Zoo of Verona, Italy, and moved in the Falconara Parco Zoo shortly after birth. The area that housed the bear was made of concrete, divided into different rooms, and equipped with windows of armored glass. The floor was in concrete and enriched with straw, leaves and dead branches. The animal was fed once a day with fruits and vegetables and once a week beef or chicken meat was administered. No other bears were hosted in the zoo and no previous health problems were recorded. Deworming were performed once a year with ivermectine.

The general conditions allowed to approach the bear without a dangerous situation occurs. In effect, the bear did not react to the approach of the people but she tried some slight reaction (feeble attempts to bite), when was touched. The bear resulted to be slightly dehydrated, appeared bilaterally blind at evaluation of the "response to the threat" and had signs of hemiparesis

involving both limbs of the left side. Anyway, deep and superficial sensitivities were preserved. Widespread tremors and nystagmus were also present. The bear appeared conscious and was able to eat. A venous sample of blood was collected from the jugular vein to analyse the hematologic parameters reported in table 1.

Table 1: Results of the hemato-biochemical analysis. Reference ranges are from Ramsay 2003 (15), except for leukocytes, white subcellular population (16) and GGT (17)

Parameter	Result	Reference range
Erythrocytes ($10^6/\mu\text{l}$)	3.89	4.17–8.93
Hematocrit (%)	22	36.8–62.7
Hemoglobin (g/dl)	8.7	11.7–59.4
MCV (fl)	56.3	44.1–93.0
MCH (pg)	18.3	15.4–33.5
MCHC (g/dl)	31.5	14.0–63.8
Leukocytes ($10^3/\mu\text{l}$)	38.6	3.9–37.6
Unsegm. neutrophils ($10^3/\mu\text{l}$)	1.0	<0.01–3.07
Segm. neutrophils ($10^3/\mu\text{l}$)	31.7	2.55–23.7
Lymphocytes ($10^3/\mu\text{l}$)	5.1	<0.01–12.4
Monocytes ($10^3/\mu\text{l}$)	0.3	<0.01–1.59
Eosinophils ($10^3/\mu\text{l}$)	0.5	<0.01–2.58
Basophils ($10^3/\mu\text{l}$)	0	<0.01–0.14
Platelets ($10^6/\mu\text{l}$)	399	134–719
Total protein (g/dl)	9.1	5.7–8.8
Albumin (g/dl)	3.3	2.7–5.4
Calcium (mg/dl)	8.9	6.6–11.5
Phosphorus (mg/dl)	5.0	3.2–9.1
Sodium (mEq/l)	133	123–150
Potassium (mEq/l)	4.8	3.6–6.1
Chloride (mEq/l)	100	94–112
Creatinine (mg/dl)	1.7	0.5–3.9
Urea nitrogen (mg/dl)	42	4–43
Cholesterol (mg/dl)	211	172–1030
Total bilirubin (mg/dl)	0.5	0.0–1.4
Direct bilirubin (mg/dl)	0.1	0.0–0.1
ALT (IU/l)	58	10–101
AST (IU/l)	158	25–203
ALP (IU/l)	111	4–210
GGT (IU/l)	432	16–176

Number of erythrocytes, haematocrit and haemoglobin resulted to be decreased causing a moderate status of anemia. The number of leukocytes was increased with most of them represented by segmented neutrophils. Values for total protein were slightly increased while GGT (gamma-glutamyl transpeptidase) resulted to have a fourfold increased activity.

Based on the clinical suspicious of central nervous system damage, a therapy including fluid administration (ringer lactate only the first day), dexamethasone sodium phosphate (4 mg/Kg, IM, BID the first day and 2 mg/Kg IM, SID in the following days), ranitidine (6 mg/Kg PO BID; Ranitidina TEVA®, Teva Pharma Italy), ceftriaxone (1.5 g, IM, SID; ceftriaxone hexal®, Hexal Spa Italy), propentofylline (3 mg/Kg, PO, BID; Karsivan®, Intervet Italia Srl), and a vitamin B complex PO, SID (Stimulfos®, Teknopharma S.p.a.) has been started. Drugs to be given parenterally, were administered by dart using a blow pipe; PO therapy was administer with food. After about a week of therapy the bear was able to stand up and walk, partially recovered the vision and ate regularly. Nevertheless, three weeks after the clinical onset, she went back in decubitus and died after 12 hours.

Necropsy revealed an irregular aspect of left ovary, and old clots were noted throughout the pelvis. The right ovary appeared normal. On gross examination, a 20×15×8 centimeter and 435 g in weight left ovarian mass was evident. Grossly, the external surface was intact and smooth, and the cut surface was gray to yellow, predominantly solid and lobulated, with a few small areas of cystic change and hemorrhage.

A 2.5 cm-sized nodule occupying the lombo-aortic lymph nodes was also observed. Additionally brain metastases were noted, characterized by multiple lesions, typically at grey white junction, profuse perilesional edema, and relatively smooth margin.

Intimal calcification of the aortic arch and scattered petechiae on the mucous membrane of the urinary bladder were also observed.

Tissue samples from tumors and all organs were fixed in 10% neutrally-buffered formalin (pH 7.4), processed for paraffin embedding, sectioned at 4 µm and stained with haematoxylin and eosin (H&E) and used also for immunohistochemical characterization. On the histological examination, the ovarian tumor was composed of epithelioid to

spindle-shaped neoplastic cells that were arranged in closely packed hollow or solid tubules with a fibrous stroma, resulting in a lobular pattern. Diffuse solid areas, microcystic pattern with eosinophilic secretion, and focal characteristic sieve-like structure were also noticed (Fig. 1). The tumor cells showed mild nuclear atypia and frequent mitotic figures. Nuclear pleomorphism and tumor necrosis was also found. Histology of brain metastases revealed a sharp interface between brain parenchyma and metastatic tumor. The neoplasm had areas of follicular architecture and areas of solid nests (Fig. 1), with tumor nuclei that were round to oval in shape with prominent nucleoli and finely granular chromatin. The neoplastic cells had abundant eosinophilic cytoplasm and mild pleomorphism. Some features of papillary carcinoma were occasionally observed. The tumor was intermixed with areas of fibrosis with hemosiderin deposition and calcification. Focal necrosis and perivascular macrophages were also noted. The adjacent brain parenchyma contained hemosiderin deposits, vascular sclerosis, and reactive astrocytes. Finally, microscopy of neoplastic nodules in the lymph nodes showed a similar histological pattern, with neoplastic cells being arranged in diffusely proliferating sheet-like cellular nests. Neoplastic cells were separated by variable amounts of fibrous stroma, but they were invasive to the stroma and lymphatic vessels. In all these three sites of neoplastic development, the neoplastic cells were largely polygonal with round to oval-shaped nuclei and abundant eosinophilic cytoplasm and prominent nucleoli with indistinct cellular borders sometimes forming rosettes, papillae, and duct-like structures; mitotic figures were observed frequently. In the lombo-aortic lymph nodes, the lymphoid tissue was mostly replaced by neoplastic cells forming a large tumor mass. In the brain, a scattered distribution of neoplastic cell aggregation of various sizes was evident, as well as larger discrete nodules.

Sections from neoplastic tissues of the ovary, brain, and lombo-aortic lymph node were immunohistochemically stained by the avidin-biotin-peroxidase complex (ABC) procedure (Vectastain Elite ABC Kit; Vector Laboratories, Burlingame, CA, U.S.A.) and examined microscopically. Details of the specific primary antibodies used and the staining results for the neoplastic tissues are summarized in Table 2.

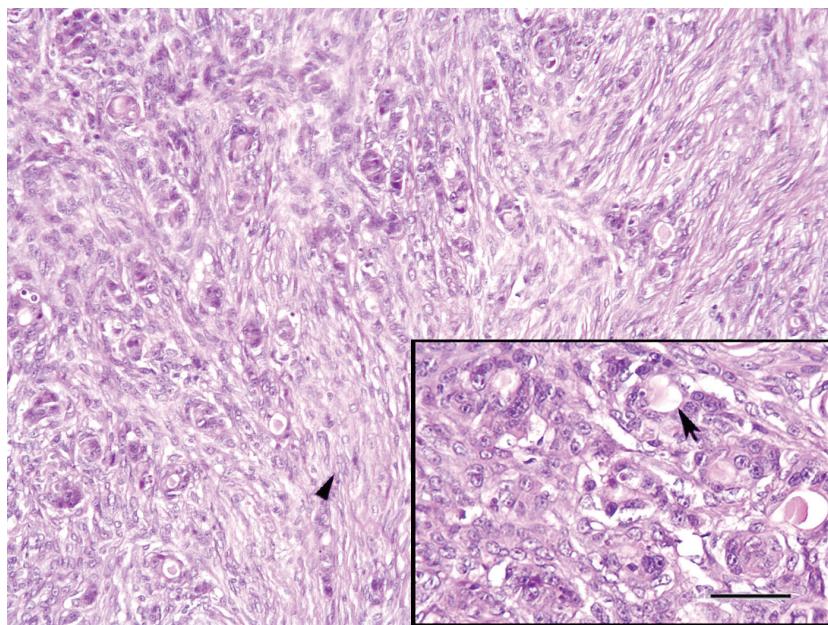


Figure 1: Low-power view of ovarian neoplastic tissue, characterized by epithelioid to spindle-shaped neoplastic cells that were arranged in closely packed hollow or solid tubules with a fibrous stroma (arrowhead); right lower insert: characteristic microcystic (sieve-like) structure with eosinophilic secretion (arrow), interspersed in a diffuse solid area. (H&E, Bar = 250 μ m; insert = 100 μ m)

Table 2: Panel of antibodies utilized for tumour characterization

Primary antibody	Antibody clone	Dilution	Antigen retrieval	Results
Vimentin	V9	1:30	none	+/-
AE1/AE3	AE1 and AE3	1:50	HMAR	+++
EMA	E29	1:50	HMAR	+
CA 125	OC 125	1:25	HMAR	+
CEA	policlonal	1:400	HMAR	-
Calretinin ^{a)}	policlonal	1:100	HMAR	++
WT1 ^{b)}	policlonal	1:100	HMAR	+

^{a)} made by ZYMED; ^{b)} made by LifeSpan Bioscience, Inc., ^{c)}HMAR = Heat Mediated Antigen Retrieval

Deparaffinized sections were blocked for endogenous peroxidase in 0.3% H₂O₂ with methanol for 30 min. Incubation of sections with the primary antibody was performed at 4°C for 16 h, followed by incubation with the biotinylated secondary antibody for 30 min, and with avidin peroxidase conjugate for 30 min at room temperature. Sections were developed in 0.05% 3,3'-diaminobenzidine/H₂O₂ solution. As positive control for each immunoreactivity, an ovary serous carcinoma, and a colonic carcinoma belonging to dog were employed. Additionally, a normal ovary and brain tissues from a brown bear (archive material) were also used. Samples from canine serous ovarian carcinoma were used for confirmation of the immunoreactivity for epithelial membrane antigen (EMA), Wilms

Tumor 1 antigen (WT-1), and Cancer Antigen 125 (CA125). Neoplastic colonic tissue was used for confirmation of the immunoreactivity for Carcino-Embryonic Antigen (CEA), and EMA. Finally normal brown bear tissue from ovary and brain were used as positive control for cytokeratins and vimentin stain.

The utilized antibodies were concentrated antibodies made by DAKOCytomation, Denmark, ZYMED Laboratories Inc., San Francisco (for Calretinin polyclonal antibody), and LifeSpan Bioscience, Inc. (for WT-1 polyclonal antibody, LS-B4578). In order to confirm immunohistochemically the diagnosis of carcinoma of the ovary, all the specimens were initially marked with vimentin to control the primary processing of the analyzed case. First we chose a panel of antibodies to help

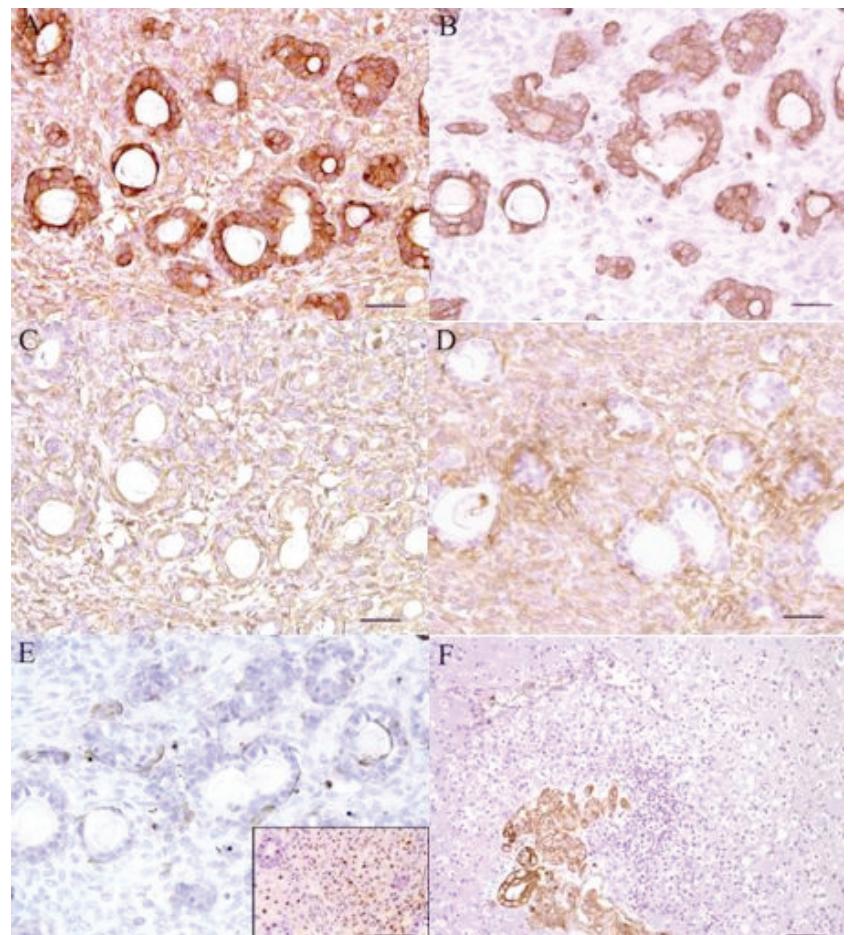


Figure 2: **A)** Diffuse and strong positivity of tumor cells, especially pseudo-cysts forming cells, for A1-A3 cytokeratins. **B)** Diffuse positivity restricted to pseudo-cysts forming cells for EMA. **C)** Calretinin diffuse and light to moderate positivity of all tumoral cells. **D)** Similar pattern of diffuse and light positivity, with the exception of the pseudo-cysts forming cells, for CA125 antigen. **E)** Substantial negativity of all neoplastic cells for CEA antigen. Note in right lower insert the strong and diffuse nuclear positivity of the neoplastic cells for WT-1 antigen. **F)** Strong positivity of brain metastasis for citokeratins A1-A3. Note the intense inflammatory reaction and edema around the neoplastic tissue. (IHC stain. Bar = 100 µm; insert and panel F = 250 µm)

establish the epithelial origin of the tumour. Thus, we opted for cytokeratin AE1/AE3, and EMA antibodies. Since there is no specific marker to indicate the ovarian origin of the tumor, the differentiation of the studied tumor from possible ovarian metastasis was realized through several associated immunohistochemical reactions. Thus, the anti-calretinin antibody was used in attempt to help, together with the CA125, CEA, and WT-1 antibodies, to eliminate a mesothelioma belonging to the peritoneal cavity. The CEA staining allowed the separation of this tumor from ovarian metastasis originating in the gastrointestinal tract. Finally, WT-1 staining was used in attempt to speculate the serous, non mucinid origin of the ovarian neoplasia. The immunostaining intensity was evaluated using a four-degree system in accordance with the model of Wauters, 1995. Immunohistochemistry stain was notable and intense for pan-cytokeratin (Fig. 2A, and F), moderate and diffuse for calretinin (Fig. 2C), light to moderate and “periacinar” for EMA (Fig. 2B), and focal and nuclear for WT-1 (Fig. 2E, insert).

Not unexpected in such a high grade carcinoma, vimentin staining was positive in a minority of epithelial cells. Calretinin staining was focally strongly positive, also in brain and lymph node metastases. Additionally, neoplastic cells showed a moderate and focal stain for CA125 (Fig. 2D), resulting consistently negative for CEA antigen (Fig. 2E). In all the neoplastic samples (primary tumor and metastases) the inconspicuous and myxoid stroma resulted strongly positive for vimentin, as expected.. On the basis of the tumor architecture, and the immunohistochemical profile, the tumor was classified, according WHO guidelines (18), as ovarian carcinoma serous type, papillary to solid.

According to WHO classification, ovarian cancers are classified in three categories: epithelial tumors (arise from cells that line or cover the ovaries); germ cell tumors (originate from cells that are destined to form eggs within the ovaries); and sex cord-stromal cell tumors (begin in the connective cells that hold the ovaries together and produce female hormones) (18). Common epithelial tumors begin in the surface epithelium of

the ovaries are divided into serous, endometrioid, mucinous, and clear cell tumors subtypes. Unfortunately, extraovarian mesotheliomas, peritoneal carcinoma, or ovarian metastatic carcinomas belonging to gastrointestinal tract, represent some tumors that are adjacent to ovarian tissues and may be viewed as ovarian cancer, complicating the histological diagnosis.

In our case, the immunohistochemical analysis of primary tumor and metastases revealed a characteristic profile of the neoplasia. Anticalretinin antibody was used (presently considered to be the best marker for mesotheliomas) together with cytokeratins, EMA and CA125 antibodies (epithelial cells markers). The immunostaining for cytokeratin AE1/AE3 was of great importance in the determination of the epithelial origin of the tumour since, for this marker, primary neoplasia and metastases were positive at the level of tumour cells (Fig. 2A, and F). The positivity of the ovarian surface epithelium for calretinin, was very helpful since it represented the positive internal control. In our case, the light cytoplasmic and diffuse pattern of calretinin positivity in neoplastic cells, suggested an ovarian surface epithelial tumor (Fig. 2C). The immunostaining was frequently diffuse and the intensity of the reaction was strong positive. The EMA expression of neoplastic cells is typical for poorly differentiated ovarian carcinomas (19), and this antibody emphasized acinar differentiation (Fig. 2B), often where it was not easily observed in haematoxylin and eosin preparations (20). Even if CA125 is not a specific marker of the ovarian origin of the tumor, some studies have shown a CA125 heterogeneous positivity in specimens of ovarian serous carcinomas (21). This type of heterogeneous staining, observed also in our case, was in favor of the ovarian origin (Fig. 2D). Since tumors with gastrointestinal origin are intense and diffusely positive for CEA (20), the negativity of this brown bear tumor supported the ovarian origin (Fig. 2E). Besides, when present, CEA expression is indicative of the mucinous type differentiation in ovarian tumors which are, at the same time, negative for CA125 (21).

Then, immunohistochemistry completed the present study of metastasizing ovarian tumor, allowing its separation from peritoneal mesotheliomas with ovarian extension and from ovarian metastasis of a primary gastrointestinal carcinoma.

The brain, along with the bone, liver, and lung, is one of the most common sites of metastasis of ovarian carcinomas. Weakness, depression, anorexia, unstable gait, alteration of the vision, slurred speech, dizziness or vertigo, head tilting are some of the neurological symptoms reported in human and animals with brain metastases (22, 23, 24) but, of course, they depend form the site of metastases implantation. Regarding clinical pathology, results were not indicative of specific diseases: many cancer patients have a mild normocytic, non-regenerative anemia associated with chronic disease. The increase in serum γ -glutamyltransferase was considered to be due to hepatic damage, but no metastases were found in the liver. Neutrophilia could be due to the reaction against the tumors and increasing in total protein could have been caused by slight dehydration.

In summary, we report here a case of malignant metastasizing ovarian tumor in a brown bear. Because of typical histological and immunohistochemical features of neoplastic cells, this tumor was diagnosed as papillary to solid serous type ovarian carcinoma. Because of the scattered distribution pattern of neoplastic nodules, the involvement of the brain and lombo-aortic lymph node was considered to be metastatic. According to these results, the presence of tumor should be considered in bears with neurological signs.

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METASTAZIRajoči KARCINOM JAjčNIKA PRI EVROAZIJSKEM RJAVEM MEDVEDU (*Ursus arctos arctos*): KLINIČNI PRIMER

Povzetek: V članku je opisan primer karcinoma jajčnika pri rjavemu medvedu. Evroazijska rjava medvedka, stara 37 let, brez mladičev, iz živalskega vrta Falconara v Italiji, je kazala klinične znake nevroloških motenj, in sicer obojestransko slepoto ter znake delne levostranske pareze obeh okončin.

Po opaženih kliničnih znakih je bila medvedka zdravljena z deksametazonom, ranitidinom, ceftriaxonom, propentofilinom, vitaminimi kompleksa B in dodajanjem tekočine. Približno po enem tednu so znaki pareze popustili, tako da je medvedka znova lahko hodila, delno se ji je povrnil vid in pričela je jesti. Kljub temu začetnemu kliničnemu izboljšanju je medvedka poginila tri tedne po pojavu bolezenskih znakov. Med raztelesbo smo našli močno povečan in tumorozno spremenjen lev jajčnik ter metastaze v regionalnih bezgavkah in možganih. Glede na značilno histološko sliko in imunohistokemične značilnosti tumorskih celic smo tumor diagnosticirali kot papilarni do solidni serozni tip karcinoma jajčnika. Zaradi razpršenega vzorca razporeditve žarišč tumorskih celic v možganih ter v ledveno-aortnih bezgavkah smo le-ta opredelili kot metastaze. V literaturi je opisanih le nekaj primerov tumorjev pri različnih vrstah medvedov (*Ursidae*), poročajo o primerih limfosarkoma, osteoma, osteosarkoma, hondrosarkoma, ploščatoceličnega karcinoma ter karcinoma žolčevodov, ščitnice, mlečne žlez in jetrnih celic. Glede na naše rezultate je potrebno pri medvedih z nevrološkimi kliničnimi znaki pri diferencialni diagnostiki pomisliti tudi na tumorje.

Ključne besede: možgani; rjni medved; metastaze; jajčnik; tumor