European Review for Medical and Pharmacological Sciences 2020; 24: 6569-6575

When a mimicker wears strange faces: description of an osteogenic melanoma arising within an ovarian teratoma with focus on its late peritoneal relapse

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Abstract. – Secondary malignancies arising within mature teratomas are a rare event, originating from malignant transformation of the tissues derived from one of the three germ cell layers.

Osteogenic melanoma is exceedingly rare histologic variant of malignant melanoma, in which the melanoma is associated to an osteogenic sarcoma component. To the best of our knowledge, first case of osteogenic melanoma arising within mature ovarian teratoma in a 30-year-old woman without evidence of a primary cutaneous or visceral melanoma. The present case showed an unusual morphological and immunohistochemical pattern and was incorrectly diagnosed as undifferentiated carcinoma. After a 15 years follow-up period, the patient presented a peritoneal recurrence histologically constituted by epithelioid cells with prominent osteoid formation and with immunohistochemical expression of melanocytic markers (S100, HMB-45).

Heterozygote Mutation V600E/E complex has been detected in the BRAF exon 15 sequence. The case was then interpreted as osteogenic melanoma.

The present case contributes to widen the spectrum of neoplasms derived from malignant transformation of ovarian teratomas and provides also new insights about the clinical behavior of osteogenic melanoma when arising outside its usual anatomical location.

Key Words:
Melanoma, Osteogenic melanoma, Ovarian teratoma, BRAF, Ovarian cancer.

Introduction

Ovarian teratomas are the most frequent germ cell tumors of the ovary composed of mature or immature tissue elements derived from the three germ cell layers: ectoderm, endoderm and mesoderm[1]. They are usually classified in two main groups: mature teratomas (benign tumors) and immature teratomas (with a tree-tiered grading system)[2].

Mature teratomas represent the most common benign germ cell ovarian tumors and are usually diagnosed in women in their second and third decades of life[1,2].

Secondary malignancies arising within mature teratomas are a rare event, occurring in approximately in 1-2% of cases, mainly in postmenopausal women[3,4]. They are thought to originate from malignant transformation of the tissues derived from one of the three germ cell layers. The most common malignant tumor observed in association with teratoma is squamous cell carcinoma[5]; other reported neoplasms include carcinoid tu-

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mors, sebaceous carcinoma, melanoma, leiomyosarcoma, adenocarcinoma of respiratory epithelium, urothelial carcinoma, small cell carcinoma, papillary carcinoma of thyroid tissue, primitive neuroectodermal tumors, osteosarcoma, oligondrendoglioma[6] and lymphomas[3,4].

Osteogenic melanoma is exceedingly rare histologic variant of malignant melanoma, in which the melanoma is associated to an osteogenic sarcoma component[7-12]. This unusual neoplasm derivates from a mesenchymal, osteosarcomatous transition of the melanoma and was first described by Urmacher in 1984[13]. To the best of our knowledge, there are no reported cases arising within ovarian teratomas.

We herein report the first case of osteogenic melanoma (OM) arising within mature ovarian teratoma in a 30-year-old woman without evidence of a primary cutaneous or visceral melanoma; patient long-term follow-up showed sixteen years later a peritoneal recurrence with the same histological features of the primary ovarian tumor.

Case presentation

A 30-year-old Caucasian woman with no significant past medical history, was referred to our institution for chronic pelvic pain and abdominal tension.

Pelvic ultrasound examination revealed the presence of a large unilateral left ovarian mass of 8 cm in largest diameter, with solid and cystic components, showing poor vascularization at color doppler examination and regular walls. These findings were suggestive for a teratomatous nature of the lesion. The contralateral ovary was not involved. There were no signs of ascites and CA-125 level was 35.80 U/ml (Reference range: <35 U/ml). Patient underwent laparoscopic monolateral salpingo-oophorectomy.

Histological examination (Figure 1) revealed a solid-cystic neoplasm with intact capsule, constituted by the co-existence of mature tissues commonly observed within ovarian teratomas (squamous epithelium, sebaceous glands), along with solid areas with unusual and peculiar mor-

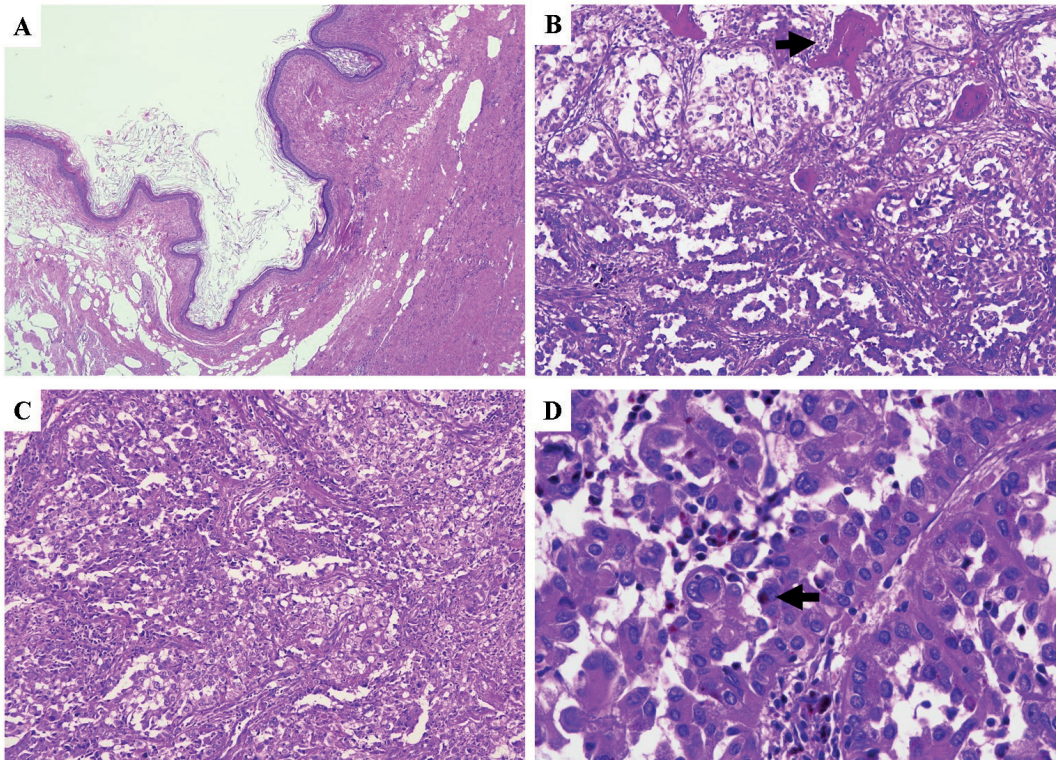

Figure 1. Morphological features of ovarian mass. **A,** Mature tissues commonly observed within an ovarian teratoma (squamous epithelium and fatty tissue) (H&E, x4). **B,** Presence of solid nests composed of atypical cells with epithelioid morphology, as well as pseudo-glandular structures lined by epithelioid cells. The intermingled stroma contained a moderate amount of osteoid-like material, consisting of irregular trabeculae of woven bone (H&E, x10). **C,** Neoplastic cells showed oval or spindle-shaped nuclei with prominent nucleoli and abundant pale to eosinophilic cytoplasm (H&E, x10). **D,** There was moderate to-severe cellular atypia, with images of cellular cannibalism. A moderate amount of brown pigment was observed (arrowhead) (H&E, x40).

phology. The solid areas of the neoplasm were composed of atypical cells with epithelioid morphology, showing hyperchromatic oval or spindle-shaped nuclei with prominent nucleoli and abundant pale to eosinophilic cytoplasm. Small nests, as well as pseudo-glandular structures and trabecular arrangements of epithelioid cells, were also observed. There was moderate to-severe cellular atypia and mitotic activity of 11 mitotes per 10 high power fields. A moderate amount of brown pigment, interpreted as hemosiderin, was observed within the neoplastic component. Moreover, the neoplastic stroma contained a moderate amount of osteoid-like material, consisting of irregular trabeculae of woven bone associated with multinucleated, osteoclast-like giant cells.

Immunohistochemical analyses were performed using formalin-fixed paraffin-embedded sections. Avidin-biotin peroxidase complex and peroxidase-antiperoxidase techniques were used. The neoplastic cells were diffusely positive for pan keratin antibody (clone AE1/AE3/PCK26, Ventana, Ventana Medical System, Inc., Tucson, AZ, USA; 1:100), CK7 (clone SP52, Rabbit Monoclonal Primary Antibody, Ventana, Ventana Medical Systems, Tucson, AZ, USA), cytokeratin 8 & 18 (CAM5.2, monoclonal; Becton Dickinson, Mountain View, CA, USA; 1:1), S-100 protein (polyclonal; Dakopatts, Glostrup, Denmark; 1:100). The neoplastic cells were negative for MELAN-A (clone A103, Ventana, Ventana Medical System, Inc., Tucson, AZ, USA), HMB45 (HMB-45, clone HMB45, Ventana, Ventana Medical System, Inc., Tucson, AZ, USA). Smooth-muscle actin (HHF35, monoclonal; Enzo Biochem, New York, NY, USA; 1:50), desmin (polyclonal; BioScience, Emmenbucke, Switzerland; 1:50), calponin (monoclonal; Dakopatts, Denmark; 1:400) alpha-inibin (Inhibin-alpha R1, Mouse Monoclonal Antibody, Cell Marque, Ventana Ref. 760-2834) alpha-Fetoprotein (alpha-Fetoprotein Rabbit Polyclonal Antibody, Cell Marque, Ventana Ref. 760-2603), Chromogranin A (Chromogranin A, LK2H10, Primary Antibody, Ventana, Ventana Medical System, Inc., Tucson, AZ, USA), Synaptophysin (anti-Synaptophysin (SP11) Rabbit Monoclonal Primary Antibody, Ventana, Ventana Medical System, Inc., Tucson, AZ, USA) and CD34 (anti-CD34, QBEnd/10 Primary Antibody, Ventana, Ventana Medical System, Inc., Tucson, AZ, USA).

Based on the morphological and immunohistochemical findings, taken into consideration the prominent epithelioid morphology and the diffuse immunohistochemical positivity for cytokeratins (AE1-AE3, CAM5.2, CK7), our final histopathological report was poorly differentiated carcinoma arising in ovarian mature teratoma.

An exploratory laparotomy was then planned, and two months later patient underwent total abdominal hysterectomy, right salpingo-oophorectomy, omentectomy, and pelvic peritoneum samplings with pelvic lymph-nodes sampling.

No pathologic lesions were observed in the uterine cavity, in omentectomy specimens and in pelvic lymph-nodes. However, pelvic peritoneum, showed the presence of neoplastic foci with the same histological features of the primary ovarian tumor.

Following surgery, the patients received chemotherapy, using cisplatin.

After a 15 years period of strict follow-up without evidence of local recurrences or distant metastases, the last abdominal TC-scan documented a suspicious lesion, located in the pre-vesical peritoneum, with solid and cystic component, measuring 4 cm in its largest diameter. These findings were highly suggestive for a recurrence of the primary ovarian tumor.

Histological examination of the peritoneal specimen (Figure 2) revealed a malignant neoplasm with solid, trabecular and pseudo-glandular pattern of growth, closely reminiscent of the primary ovarian tumor, composed of atypical epithelioid cells, showing hyperchromatic with prominent nucleoli and abundant pale to eosinophilic cytoplasm. Notably, the recurrent tumor showed abundant brown-black pigment within the cytoplasm of neoplastic cells, and given its positivity for Fontana Masson stain, it was interpreted as melanin. Moreover, numerous irregular trabeculae of woven bone surrounded by atypical epithelioid cells, associated with multinucleated, osteoclast-like giant cells, were observed in the neoplastic stroma. These histological features were highly suggestive for a high-grade osteogenic sarcoma.

The immunohistochemical profile of the recurrent tumor (Figure 2) showed slight differences from its ovarian counterpart. In detail, only a focal positivity for cytokeratin antibodies (AE1-AE3, CAM 5.2, CK7) was observed in approximately 10 to 20% of the tumor cells; whereas a diffuse positivity for S100 and HMB-45 was observed. Negative staining for MELAN-A was observed.

Taking into consideration, the presence of abundant melanin pigment within neoplastic epithelioid cells, the diffuse positivity for melano-

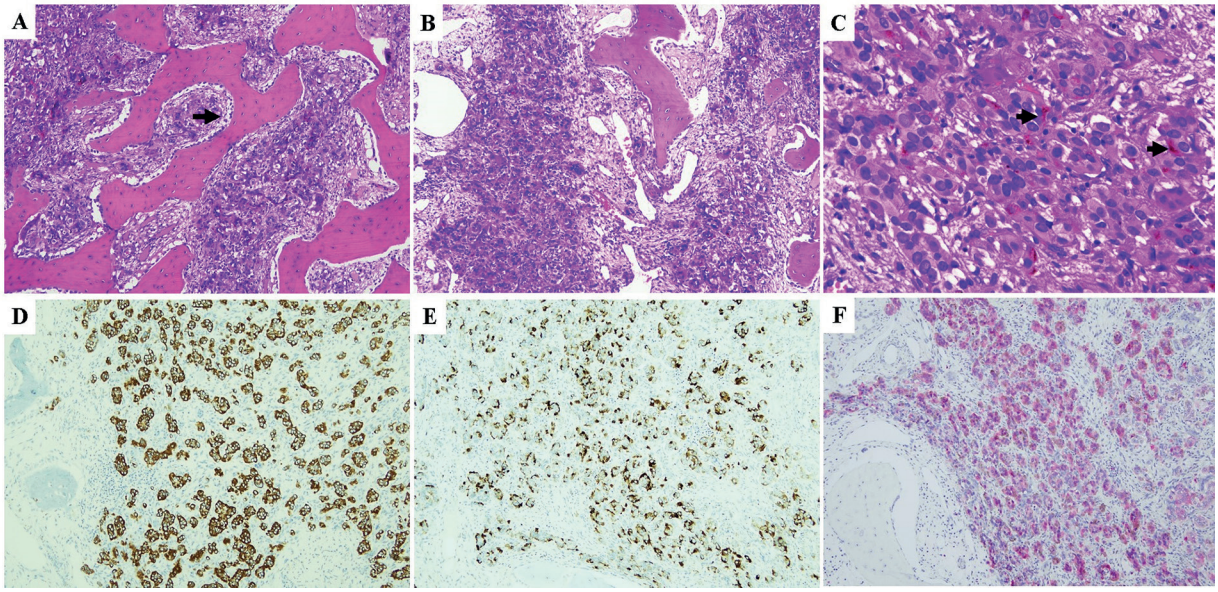

Figure 2. Morphological and immunohistochemical findings of peritoneal relapse. **A-B,** The peritoneal sample revealed a malignant neoplasm with solid and pseudo-glandular pattern of growth. Numerous irregular trabeculae of woven bone surrounded by atypical epithelioid cells (arrowhead in **A,** associated with multinucleated, osteoclast-like giant cells were observed (**A** H&E, x10; **B** H&E, x4). **C,** The moderately atypical cells showed hyperchromatic nuclei with evident nucleoli and abundant pale to eosinophilic cytoplasm. Notably, the recurrent tumor showed abundant brown-black pigment (arrowhead) (H&E, x40). **D-E-F,** Tumoral cells showed positivity for cytokeratin antibodies (AE1/AE3) and for melanocytic markers: HMB-45 and S100 (**D** AE1/AE3, LSAB, x10; E: HMB45, LSAB, x10; F: S100, performed by Fast Red Chromogen Kit, x10).

cytic markers (S100, HMB-45), the focal positivity for cytokeratins as well as the presence of an osteogenic sarcomatous component, we reinterpreted the recurrent tumor as well as the primary ovarian tumor, as a rare variant of malignant melanoma with osteogenic sarcomatous component and aberrant expression of cytokeratins: 'osteogenic melanoma'.

Mutational analysis of BRAF was then performed. DNA was extracted from three 10 µm-slides from paraffin-embedded tissues using QIAamp DNA FFPE Tissue Kit (Qiagen, Milan, Italy), following the manufacturer's protocol. In order to minimize contamination by normal cells, the tumor areas dissected for DNA extraction contained at least 70% of tumor cells. BRAF exon 15 and exon 11 were amplified using the same primers and polymerase chain reaction (PCR) conditions previously described[14]. Briefly, DNA (100-200 ng) was amplified in a mixture containing 1 × PCR buffer (20 mM Tris, pH 8.3; 50 mMKCl; 1.5 mM MgCl2), deoxyribonucleotide triphosphates (200 mM each), primers (20 pM each), and 0.5 U GoTaq (Promega, Madison, WI, USA,) in a final volume of 25 µL. PCR conditions were as follows: initial denaturation at 95°C for 8 minutes followed by 35 cycles at 95°C for 40 seconds, 55°C for 40 seconds, and 72°C for 40 seconds. After visualization onto agarose gels, PCR products were treated with ExoSAP-IT (USB Corp, Cleveland, OH, USA) following the manufacturer's protocol, amplified with the BigDye Terminator cycle-sequencing kit (version 3.1; Applied Biosystems, Foster City, CA, USA) using forward and reverse primers, and sequenced with an ABI PRISM 3100-Avant Genetic Analyzer (Applied Biosystems, Foster City, CA, USA). Water was used as a negative control.

Heterozygote Mutation V600E/E complex has been detected in the BRAF exon 15 sequence (Figure 3). Finally, an accurate clinical and radiological examination excluded the presence of simultaneous visceral or cutaneous suspicious lesions.

Discussion

Osteogenic melanoma is a rare variant of malignant melanoma in which an osteogenic high-grade sarcoma is found in association with melanoma[7-13]. The first case was reported in 1984 in

a paper by Urmacher[13]; the author documented the presence of an osteogenic component in a recurrence of a spindle cell melanoma from the retroauricular region[13]. Since then, additional 25 cases have been reported[10]. The most accredited theories for the uncommon association between melanoma and osteoid production include: i) common origin of melanocytes and mesenchymal cells from primitive neural crest cells; ii) metaplastic conversion of melanocytes to sarcomatous cells (similarly to metaplastic breast carcinoma and malignant mixed mesenchymal tumors of the uterus; iii) the traumatic theory which postulates that osteoid may be formed as a reparative response to injury; in fact, many osteogenic melanomas have been documented in recurrences following prior trauma, including surgical procedures[15]. Moreover, the ossification phenomenon has been reported in melanomas that recurred in areas of previous surgical trauma[15,16].

Most reported tumors occurred in acral skin or nasal/oral mucosa of middle-aged patients with no sex predilection; however, no cases have been reported to arise within ovarian teratoma or in the peritoneal cavity. In reports with available follow-up information, only three patients died for the disease at 6 months, 20 months, and 48 months respectively, following the histological diagnosis[7,13,15]. Other eight patients, with available follow-up, were alive without disease for periods ranging from 2 months to 100 months[7,12].

The present case represented a diagnostic challenge, since the unusual location within an ovarian cystic teratoma, the morphology (pseu-

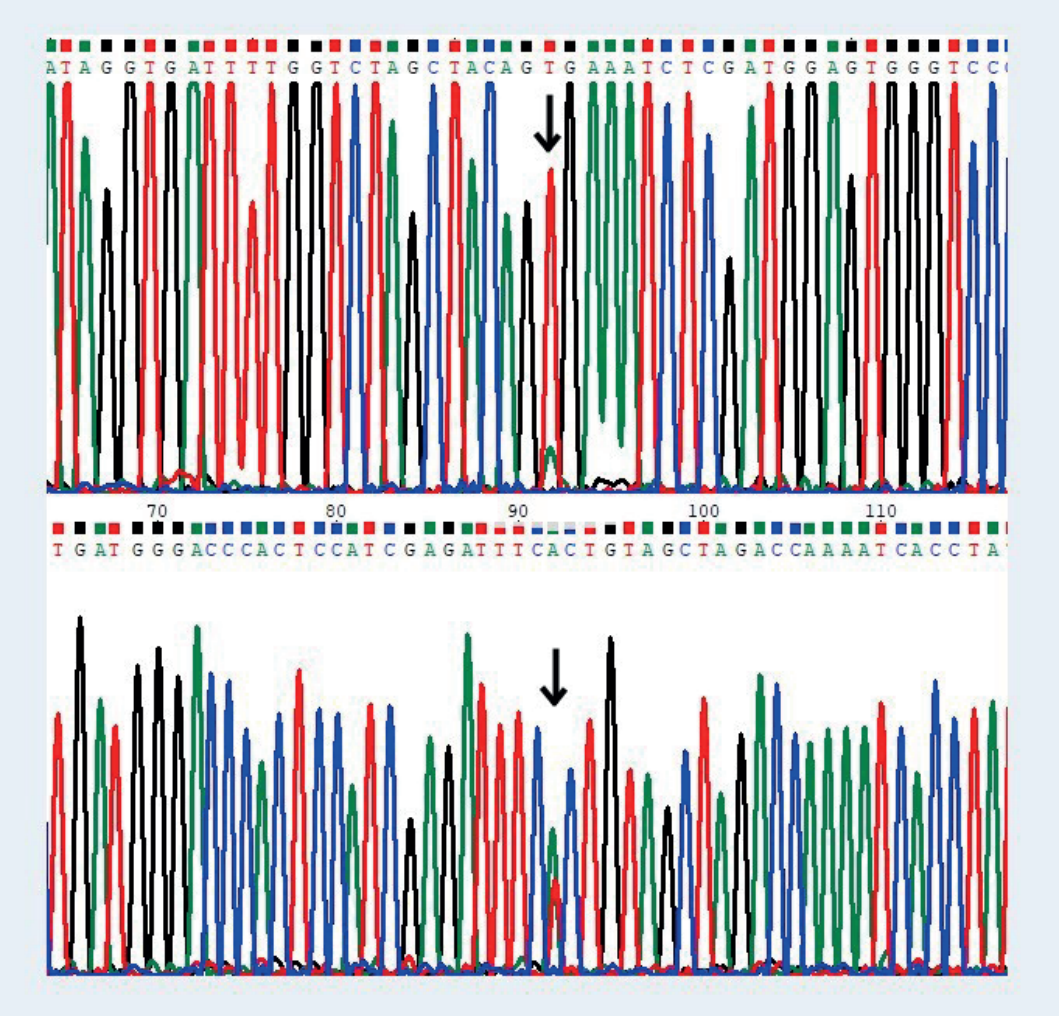

Figure 3. Mutational BRAF status. The figure shows the partial sequence of BRAF gene with the V600E (c.1799T.A) mutation (black arrow) in the primary melanoma, arisen within an ovarian teratoma (above) and in the peritoneal relapse (below).

do-glandular and trabecular pattern), and the diffuse immuno-expression of cytokeratin antibodies along with focal expression of S100 protein lead to an erroneous diagnosis of undifferentiated carcinoma. However, the correct diagnosis was achieved in the peritoneal recurrence, 15 years later. In fact, the abundant osteoid production along with the diffuse expression of melanocytic markers were highly suggestive for the diagnosis of osteogenic melanoma.

Apart from poorly differentiated carcinoma, the main differential diagnosis for the present case was extra-skeletal osteosarcoma. However, the presence of epithelioid cells with prominent nucleoli and the diffuse expression of S-100 and HMB-45, supported the diagnosis of melanoma. Clear cell sarcoma (CSS) was also ruled out despite its melanocytic differentiation, given the osteoid production and the absence of clear cell changes. Malignant peripheral nerve sheath tumor, epithelioid variant (EMPNST), and ossifying fibromyxoid tumor were also ruled out despite the reported S100 positivity, since other melanocytic markers (MELAN-A, HMB-45) are usually negative allowing exclusion of such hypotheses.

From a molecular point of view, our case showed heterozygote mutation V600E/E complex in the BRAF exon 15 sequence, which is found in approximately 50% of melanomas[17].

Nodular histopathological subtypes, age at diagnosis of the primary tumor (≤50 years), the presence of an occult primary melanoma, the prevalent onset in non-sun-exposed sites are some of clinico-pathological features more significantly associated with a BRAF mutation[18], also observed in the present described case.

According to literature data *BRAF* mutant-type melanoma patients can nowadays receive benefit from Vemurafenib, an excellent example of personalized targeted therapy[19].

Conclusions

Melanoma is one of the great mimickers in pathological diagnosis, since its remarkable phenotypic plasticity[20,21]. Generally, some morphological details, immunohistochemistry and clinical history are helpful in supporting the diagnosis, ruling out the differentials[21,22]. However, sometimes (first of all in recurrences), melanoma may lose the expression of typical melanocytic markers and conversely show positivity for non-melanocytic lineage markers[23-25]. In this way, the possible diverse unusual morphologies and the atypical immunoprofile pose a diagnostic dilemma that can lead to an erroneous diagnosis of poorly differentiated carcinoma or sarcoma.

We herein reported, for the first time, an osteogenic melanoma arising within ovarian mature teratoma which recurred in the peritoneal cavity after 15 years of strict follow-up, histologically characterized by different morphologies and aberrant cytokeratin expression.

We believe that the observation of cells that express both lineage markers (S100 and keratin) may in part be due to the occurrence of additional genetic alterations, epigenetic cellular reprogramming or to an actively ongoing trans-differentiation process.

Moreover, the present case contributes to widen the spectrum of neoplasms derived from malignant transformation of ovarian teratomas and also provides new insights about the clinical behavior of osteogenic melanoma when arising outside its usual anatomical location.

Contributions

Giuseppe Angelico, Angela Santoro and Frediano Inzani were responsible for gathering data and manuscript design; Giuseppe Angelico and Angela Santoro also wrote the text. Maurizio Martini and Nicoletta D'Alessandris performed the molecular analysis. Saveria Spadola, Michele Valente, Damiano Arciuolo and Stefania Sfregola added discussion to the results. Gian Franco Zannoni, Antonino Mulè and Michele Valente were responsible for histopathological diagnosis. Gian Franco Zannoni was responsible for work supervision and provided manuscript review. Giovanni Scambia performed the surgical procedures. All authors read and approved the manuscript final version.

Ethics Declarations

This study was performed in accordance with the ethical standards defined by Fondazione "Policlinico Agostino Gemelli" – IRCCS, Rome, Italy.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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