Choroidal melanoma metastasized to the ovary: case report and review of the literature

V.D. Mandato[1], B. Kobal[2], A. Di Stefano[2], J. Sinkovec[3], A. Levicnik[3], G.B. La Sala[1], S. Rakar[2]

[1]Department of Obstetrics and Gynecology, Arcispedale S. Maria Nuova di Reggio Emilia, University of Modena and Reggio Emilia (Italy)
[2]Division of Gynecology and [3]Pathology Unit, Department of Obstetrics and Gynecology and University Medical Centre Ljubljana, Ljubljana (Slovenia)

Summary

Background: Malignant melanoma metastases to the female genital tract in only 2.5% of cases. Melanoma is characterized by clinical variability and unpredictable biological behavior with long remissions and relapses that develop rapidly. *Case and review:* A 57-year-old woman was admitted for hypogastric pain and weight loss. She had presented enucleation of the right eye six years before for malignant choroid melanoma. Gynaecological examination revealed enlarged ovaries. Bilateral salpingo-oophorectomy, hysterectomy, and omentectomy were performed. Final pathology diagnosed a choroidal metastatic melanoma (CMM). The patient died seven months later. Only seven cases of CMM have been reported in the literature. Patients affected by CMM ranged in age from 38 to 83 years (median 51.2 years), the time to relapse ranged from 3-25 years (median 51.2 years), the size of the cysts ranged from 4-17 cm (median 9.7 cm) and the survival period ranged from 2-14 months (median 8.1 months). *Conclusion:* Malignant melanoma is misdiagnosed because of lack of discriminatory symptoms, increased tumor markers, characteristic imaging findings and the capacity to mimic other tumors. Today CMM still represents a challenge for gynecologic oncologists.

Key words: Choroidal melanoma; Ovary; Metastasis; Diagnosis; Staging; Treatment.

Introduction

Melanoma is a malignant neoplasm of neuroectodermal origin characterized by melanin production that usually affects the skin, adrenal glands and ocular choroid. It is characterized by clinical variability and unpredictable biological behavior with long remissions and relapses that develop rapidly. Metastases to the lungs and liver are the most common cause of death.

Malignant melanoma (MM) accounts for only 3% of cancers that affect female patients and results in less than 1% of cancer deaths [1]. However, in recent years its incidence has been increasing. Primary MM of the reproductive tract usually arises from the vulva (3-7% of MM) [2, 3], secondary or primary melanomas of the upper genital tract are very rare [4].

To the best of our knowledge, only seven cases of ovarian metastasis from previous choroidal melanoma have been reported in the literature. Patients affected by CMM ranged in age from 38 to 83 years (median 51.2 years), the time to relapse ranged from 3-25 years (median 51.2 years), the size of the cysts ranged from 4-17 cm (median 9.7 cm) and the survival period ranged from 2-14 months (median 8.1 months) [5-11].

In this report we present the eighth case of choroidal metastatic melanoma (CMM) of the ovary treated at our department describing the clinical aspects and histopathological features, while discussing the differential diagnosis of MM affecting the ovary.

Revised manuscript accepted for publication February 28, 2009

Case Report

Clinical history

A 57-year-old postmenopausal woman was admitted for hypogastric pain and weight loss (5 kg in 1 month). Her history was characterized by enucleation of the right eye six years before for malignant choroid melanoma. Gynecological examination revealed enlarged ovaries that had a polycystic appearance on ultrasound scan. Free fluid was in the Douglas pouch. Tumor markers (CA 125, CA 15-3, CA 19-9, CEA, AFP, TPA, NSE and PSA) were within the normal range. The patient underwent midline laparotomy for ovarian cancer. Cytologic evaluation of the free fluid aspirated from the Douglas pouch did not reveal malignant cells. At laparotomy two blackish enlarged ovaries were found. The left (11 x 8 x 5 cm) and the right ovary (4.5 x 2 x 5 cm) were resected. The frozen section revealed metastases of CMM. Macroscopically the omentum showed tiny (1-2 mm), dark-brownish petechial lesions, and omentectomy was therefore performed. Further systematic intraabdominal exploration revealed a pancreatic mass and an enlarged metastatic paraaortic lymphnodes, considered unresectable by the surgeon. An extrafascial hysterectomy was also performed.

Because of the advanced metastatic disease and poor prognosis the patient received only a symptomatic and palliative therapy. She died seven months later.

Clinical methodology and findings

The resected lesion was fixed in 10% buffered formalin and multiple extensively sampled sections were then routinely embedded in paraffin and stained with hematoxylin and eosin (Figures 1-2). Cytoreduction procedures were total abdominal hysterectomy with bilateral salpingo-oophorectomy and total omentectomy.

Fig. 1

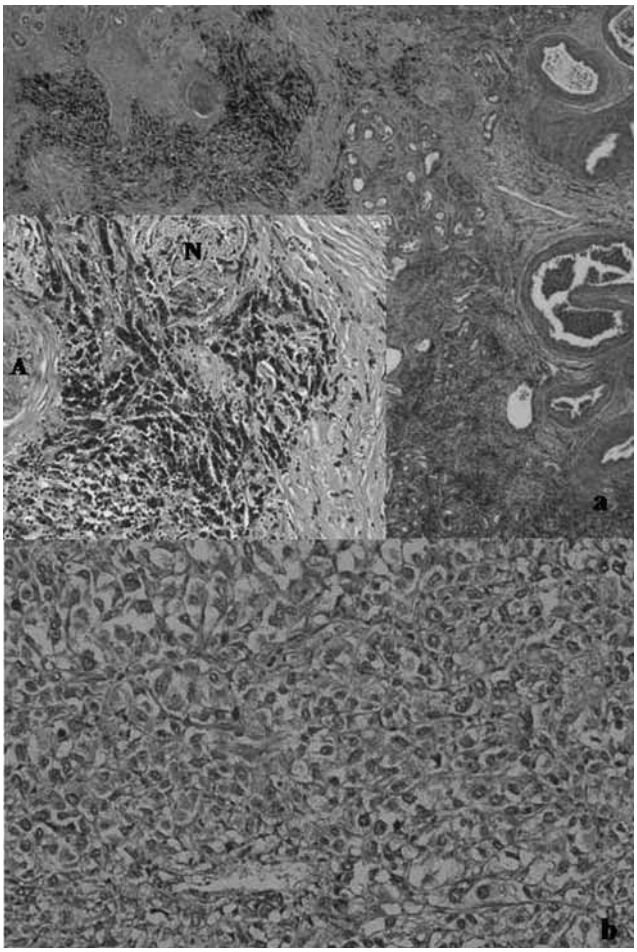

Fig. 2

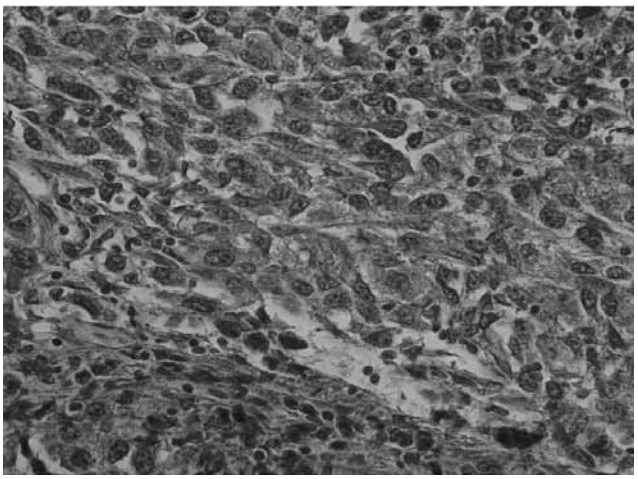

Fig. 3

Figure 1. — a: Malignant melanotic cells with melanin pigment in the ovarian medulla. Perineurium is infiltrated by MM cells [artery (A), nerve (N)]. b: Tumor cells with signet-ring appearance and clear cytoplasm.
Figure 2. — Nested pattern is also present: melanoma cells with epitheloid-like appearance and spindle shaped cells tending to form groups and surrounded by fibrous septa.
Figure 3. — Macroscopic appearance of the dark brownish ovary.

Pathological findings

Final pathology diagnosed metastases of CMM in both ovaries and the omentum. Diagnostic esophagogastroscopy and a transabdominal US examination confirmed the metastatic involvement of the stomach and pancreas.

Histological findings

The left ovary, measuring 4 cm, had a smooth surface and showed cystic lesions filled with a clear fluid and showing a smooth surface with dark spots (Figure 3). The right ovary showed small multilocular cystic lesions, 2 mm in diameter, filled with clear fluid and with a smooth internal and external surface. Microscopic examination revealed bilateral serous cystadenofibroma and metastases of CMM.

The omental sample showed an enlargement of 1 cm and two smaller dark blue areas of 0.5 mm; the cut surface revealed a slightly nodulated, black tumor. Microscopic investigation diagnosed metastases of CMM.

Discussion

Involvement of the female genital tract from extragenital cancers is uncommon. The most common extragenital cancers metastasizing to the female genital tract are breast and gastrointestinal carcinomas [12]. Malignant cutaneous melanoma accounts for only 2.5% of cases metastasizing to the female genital tract and the ovaries are most often affected (75-80% of the cases) [13].

The rarest melanoma metastasizing to the ovary is choroid melanoma. To our knowledge only seven cases have been completely described in the literature [5-11] (Table 1).

Ocular melanoma presents an incidence in the general population ranging from 0.5-1 per 100,000 [10, 14, 15], 50% of patients die in 15 years [12, 10], and 20% metastases occur within five years [16]. It has a latent progression with metachronous metastasis up to 42 years from the first diagnosis [17].

Table 1. — *Characteristics of the patients with ovarian metastasis from previous choroidal melanoma.*

Author	Age	Primary	Symptoms	Ovarian	Other	Imaging	Tumor	IHC	Treatment	Follow-up
Dawson *et al*. [5]	38	Right eye (choroid spindle cells, pigmented)	Pelvic mass size of an orange	Left ovary (4 y 5 mo, spindle cell)	Right arm Sixth dorsal spine (14 y 5 mo)	–	–	–	BSO	NED (9 mo)
Ben David *et al*. [6]	62	Left eye (choroid)	Vaginal bleeding left lower abdominal pain nausea	Left ovary (25 y, epitheliod cells, pigmented)	Omentum small and large bowel (25 y)	Semisolid pelvic tumor (USG)	–	–	TAH+ BSO+ OM	CX
Thiery *et al*. [7]	35	Right eye	Vomiting, diarrhea, weight loss, abdominal swelling	Both ovaries (15 y 3 mo)	Abdomino pelvic (15 y 3 mo)	–	–	–	BSO	CX DOD (8 mo)
Santeusanio *et al*. [8]	47	Right eye (choroid spindle cells, pigmented)	Pelvic pain	Right ovary (14 y, 17 x 10 x 6.5 cm spindle cells)	No other site	Right adnexal mass (USG) NR	NR	S-100 HMB-45 MART1 vimentin Ki 67 (< 10%)	TAH+BSO+ appendectomy + random peritoneal and omental sampling	(14 mo)
Rey-Caballero *et al*. [9]	38	Left eye (choroid)	Hypo gastric pain vaginal spotting	Left ovary (9 y, 7 cm)	No other site	Round solid mass in the Douglas	–	–	TAH+BSO+ LFN+OM	Interferon NED (7 mo)
Coutts *et al*. [10]	83	Left eye (choroid, epithelioid and spindle cells)	Vaginal bleeding	Right ovary (3 y, nodules)	Systemic widespread (3 y)	Autopsy	–	–	Palliative care	DOD (2 mo)
Bloch-Marcotte *et al*. [11]	50	Left eye (choroids)	Abdominal pain	Right ovary (20 y, 4 cm)	Liver	Heterogeneous Ovarian soft tissue (CT)	–	Melanin A HMB-45	Laparoscopic ovariectomy	CX (2-5 mo)
Index case	57	Right eye	Hypo gastric pain body weight loss (5 kg in 1 mo)	Both ovaries [6 y, left ovary (11 x 8 x 5 cm), right ovary (4.5 x 2 x 5 cm) epithelioid and spindle cells]	Abdomino pelvic (6 y)	Polycystic mass, free fluid in the Douglas pouch (USG)	NR	–	TAH+BSO+ omental sampling	DOD (7 mo)

TAH: total abdominal hysterectomy; BSO: bilateral salpingo-oophorectomy; OM: omentectomy; LFN: lynphadenectomy; Y:years; Mo:months. NR: normal range; USG: ultrasonography; CT: computer tomography; NR: normal range; IHC: immunochemistry ; CX: chemotherapy; NED: no evidence of disease, DOD: died of disease.

Although occult metastasis to the ovary from a primary MM has been reported in up to 18% of women in autopsy studies [18], symptomatic MM is very rare.

It is predominantly diagnosed in women in reproductive age (80%) (average age 35 years), usually unilateral and associated with a poor prognosis [19]. Women of reproductive age may be more prone to metastatic ovarian involvement because the higher blood flow to the premenopausal ovary [20]. The recurrences often occur after a long period of remission (10 years after the initial diagnosis), probably because female hormones might influence the natural history of melanoma [18]. Also, clomiphene has been suspected of increasing the risk of ovarian metastatic melanoma but data have not been able to support this hypothesis [21].

Preoperative diagnosis of ovarian MM presents some difficulties, and usually the diagnosis is made retrospectively after laparotomy.

Similarly to ovarian MM, also CMM can present as a solitary ovarian metastasis [8, 9, 22], or as in the present case as widespread disease [5-7, 10, 11].

Most metastatic tumors involve both ovaries, conversely, ovarian metastases from melanoma are mostly unilateral [19]. On the contrary, Thiery *et al*. [7] reported a CMM involving both ovaries, as in the present case (Table 1).

Our patient showed diffuse intraabdominal metastatic disease six years after the initial surgery of the primary choroid melanoma even though serum levels of tumor markers were within the normal range.

US examination did not discriminate the ovarian mass; in fact in our case, as reported in the literature, ovarian metastases at US examination presented with images similar to those of primary tumors, multilocular masses and without typical findings that can differentiate them [23]. Magnetic resonance imaging could characterize the lesion only in the presence of a conspicious amount of melanin which causes a peripheral high signal change on T1-weighted images (in contrast to central increases of activity in dermoids and endometriomas), which happens only in one-third of patients [14, 24].

However, when a relapsed melanoma is suspected a positron emission tomography (PET) scan should be performed to detect subclinical metastases and to stage the disease [25].

Melanoma of the ovary represents diagnostic difficulties because the tumors do not have a consistent appearance, and on histology they can be mistaken for germ cell and sex cord stromal tumors [19, 26, 27]. Steroid cell tumors in particular show as abundant eosinophilic cytoplasm as melanomas but they are usually not as mitotically active as melanomas. Although steroid cell tumors may contain lipofuscin pigment, teratomatous elements (primary melanoma), spindle cells and melanin pigment are supportive of melanoma [26]. Moreover immunohistochemistry using melanocytic and sex cord-stromal

markers, such as inhibin and calretinin [28], is likely to be useful, but ovarian sex cord stromal neoplasms and steroid cell tumors are not uncommonly positive with some melanocytic markers, including S-100 and melan-A [29-30]. MM of the ovary rarely shows positivity for inhibin or calretinin [31]. On the contrary, the most specific melanocytic marker HMB 45 may occasionally be positive in ovarian steroid cell tumors [29]. In our cases the diagnosis was made only after laparotomy because of a typical picture of metastatic melanoma of macroscopic and microscopic findings (Figures 1-3).

The diagnosis of primary ovarian MM requires the absence of a primary extraovarian tumor, the detection of an unilateral ovarian tumor with teratoid elements, histological evidence of melanocyte junctional activity, and a good correlation of patient age and symptoms with the cases reported in the literature [26].

The principal treatment is surgery ranging from an ovarian cystectomy to extensive debulking. Medical therapy consists of chemotherapy and immunotherapy. Cisplatin and dacarbazine are the most effective drugs used in patients with persistent or recurrent disease, whereas alfa-interferon and interleukin-1 are promising in metastatic melanoma [15, 32-34].

Even if surgery and use of cisplatin-based chemotherapy appear to improve the outcome, the total response rates of melanoma to adjuvant chemotherapy remain within range of only 20%, with a complete response rate of less than 10% [35].

Hence, several combined therapeutic strategies are commonly adopted because CMM mimics primary ovarian cancer and leads to unnecessary aggressive cytoreductive surgery (Table 1). Secondary ovarian involvement should be diagnosed preoperatively to avoid over-treatment and to provide adequate palliative therapy.

In conclusion, melanomas of the ovary are very rare and very ominous. It is important for the gynecologist to suspect melanoma of the ovary when a patient with a history of a previous malignant melanoma (cutaneous, mucosal) has symptoms such as bleeding, pain, swelling, and abdominal mass.

Malignant melanoma of the ovary represents several diagnostic problems. It is often misdiagnosed because of non discriminatory symptoms, normal levels of tumor markers, non characteristic imaging findings and the capacity to mimic other tumors. Furthermore, in cases of CMM, because of its latency, the diagnosis of metastasis from a melanoma is difficult because the patient may have been in remission for many years or because the antecedent is unknown. Although the first case of choroidal metastatic melanoma of the ovary was described in 1922 [5], CMM still today represents a challenge for gynecologic oncologists.

Acknowledgments

We gratefully appreciate the help of the Cancer Registry of Slovenia for data about patient survival.

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Address reprint requests to:
V.D. MANDATO, M.D.
Department of Obstetrics and Gynecology
Arcispedale S. Maria Nuova
di Reggio Emilia
University of Modena
and Reggio Emilia (Italy)
e-mail: VincenzoDario.Mandato@asmn.re.it