Sister Mary Joseph Nodule or Umbilical Cutaneous Metastasis Coexisting with Medium Differentiated Endometrioid Endometrial Carcinoma

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***Abstract*—A 82 years hypertensive, obese, 1 delivery, menopause at 47 yrs, non-smoker, with history of vaginal bleeding in January 2018, is sent by the dermatologist for an irregular umbilical tumor of 2/1 cm, recurrent at 6 weeks post-ablation, microscopically considered as a carcinomatous metastasis. Abdomino-pelvic MRI rises the suspicion of uterine carcinoma, which is confirmed by endometrial biopsy. It is done extrafascial total hysterectomy with bilateral adnexectomy and pelvic nodes lymph-adenectomy and ablation of a skin-adipose-conjunctive peri-umbilical area of 5/4 cm. There were no peritoneal metastases, or other viscera abnormalities. The optic microscopy shows moderate differentiated endometrioid endometrial carcinoma, with areas of squamous differentiation, with invasion of the external myometrial half, without peritoneal invasion, with vessels metastatic embolisations, positive pelvic lymph nodes with moderate differentiated endometrioid endometrial carcinoma and desmoplastic reaction, left ovary with mature teratoma. In the skin fragment there is neoplazic invasion of cribriform and tubular pattern, areas of squamous differentiation, and vessels with neoplazia emboli. Sister Mary Joseph Nodule was characterized by Hamilton Bailley (1949), after the initial description of William Mayo(1928) from the first observations of the assisstant catholic nun Mary Joseph Dempsey at Saint Mary's Hospital, Rochester, Minnesota (SUA). The nodule is associated to malignancyes with origin in the gastro-intestinal, respiratory, urinary, and genital tract- primary ovarian and endometrial cancers. The umbilical invasion may be due to direct vessels' embolization by malignant cells, and via the lymph vessels which run along the obliterated umbilical vein, or via the remnant structures of the falciform and umbilical ligaments. Sister Mary Joseph Nodule has a bad prognosis, the patient is under oncological follow-up, after radiotherapy and on hormone therapy.**

Keywords—cutaneous metastases, nodule, endometrioid/serous endometrial carcinoma

I. *Introduction*

The umbilical lesion known since more than 150 years as a sign of an abdominal malignancy, and named "Sister Mary Joseph" Nodule (SMJN) is more frequent discovered in the last 20 years,. being described around 400 cases up to 2006 [1]. In case of a malignant umbilical tumor, 75% correspond to a "Sister Mary Joseph nodule"., and the cutaneous secondary umbilical tumor may appear previous, during or after the diagnosis of the primitive tumor, diagnosed or not.

II. *Case Report*

A 82 years old patient, 1 birth, no abortion/miscarriage, menopause at 47 years, BMI> 30, with hypertension, and hyperuricemia, non smoker, nothing relevant in. patient's family history, and in her recent medical history: vaginal blood loss with short duration and low amount, 5 months previous to the gynecological presentation, where she is sent by the dermatologist for a recurrent umbilical irregular tumour sized of 2/1 cm, with reappearance at 6 weeks after excision, and microscopically proved to be a carcinomatous metastasis, from an unknown organ. At the moment of first gynecological presentation (July 2018) the patient had a larger uterus for the age, with reduced mobility, and an solid adnexal mass of 6 cm in the largest diameter, and an endometrial thickness of 8 mm, with irregularities and an ovarian teratoma at sonography. MRI reports normal uterine shape and contour, endometrial enlargement of 6.8 mm from the fundus to isthmus, an ovarian cyst of 7/4.5 cm suggestive for dermoid cyst, enlargement of left external iliac nodes, and no metastases in the abdominal and pelvic cavities. The laboratory reveales mild anemia, high levels of uric acid, and of human epididymis protein 4 (HE4), recognized as a marker for serous ovarian carcinoma, fact which can be explained by hyperuricemia, normal EKG, chest X ray in the limits of age. Endometrial pipelle biopsy confirms the suspicion of endometrial carcinoma.

It is done abdominal laparatomy, and it is discovered an enlarged uterus according to patient's age, an ovarian cyst of 2/2 cm, and minimal abdominal fluid with negative cytology, no peritoneal metastasis or other viscera abnormality. It is done ablation of an area of 5/4 cm from the parietal wall, containing peri- and subumbilical cutaneo-conjuctivo- adipous tissue,

centered by the umbilicus and the umbilical metastatic tumor, total extrafascial hysterectomy, bilateral adnexectomy, and pelvic nodes lymphadenectomy. The optic microscopy reveals

- uterine wall with medium and weak differentiated endometrioid endometrial carcinoma, with dermoplastic reaction, and compact areas of squamous differentiation (Fig. 1; A; B), and small pseudoglandular structures, with secondary branches in a reduced stromal mass

- invasion of the external half of the myometrium, without peritoneal invasion, and vascular emboli (Fig. 1, C; D)

- large invasion of the isthmus and the endocervix

- pelvic nodes with metastases of medium differentiated endometrioid endometrial carcinoma with dermoplastic reaction

- left ovary with an mature dermoid cyst

The cutaneous fragment contains a protuberant tumor with marked acantosis and tumoral epithelial psudoglandular branched islands and solid areas of scoamous differentiation, similar to uterine tumor, and neoplastic emboli in the vessels

The immunohistochemistry of the uterus shows: ER 90% + in uterine tumor cells, PR difuse + in the uterine wall and cervical stroma; Ki67 + in 65% of uterine tumor cells, WTI – in the tumor, and zonal + in endometrial stroma, The immunohistochemistry of the skin fragment shows: P40 + in the epiderm; Ki 67 + in 70 % of skin tumor cells; ER + in 90% of skin tumor cells; PR + in 90% of skin tumor cells. As a result, the conclusive diagnosis was a stage IV endometrial carcinoma (FIGO endometrial cancer staging).

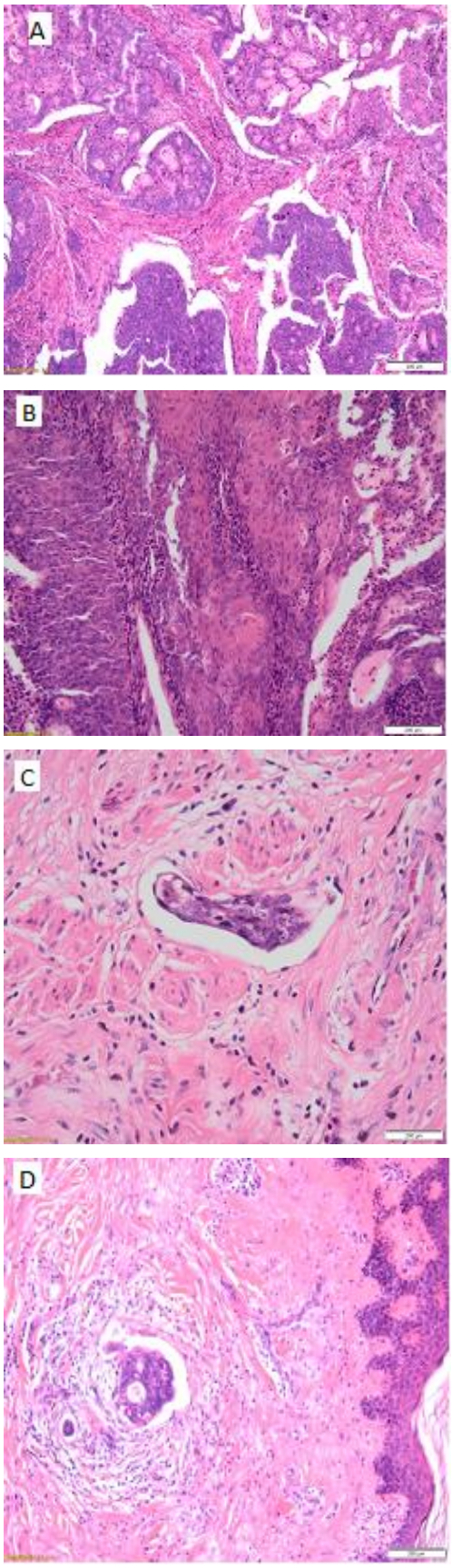

Figure 1. A: Weak and medium differentiated endometrioid endometrial carcinoma. B: Compact areas of squamos differentiation. C: Thrombus in the uterine vessel. D: metastatic embolus in the derm. HE stain, x 40. ("Dr I Cantacuzino" Pathological Department)

The postoperative evolution is normal of surgical point of view, followed by radiotherapy with 45Gy/25 fractions plus brachitherapy 20Gy, and Megasin® 160mg/day from January .2019, with normal abdominal appearance in March 2019 (Fig. 2)

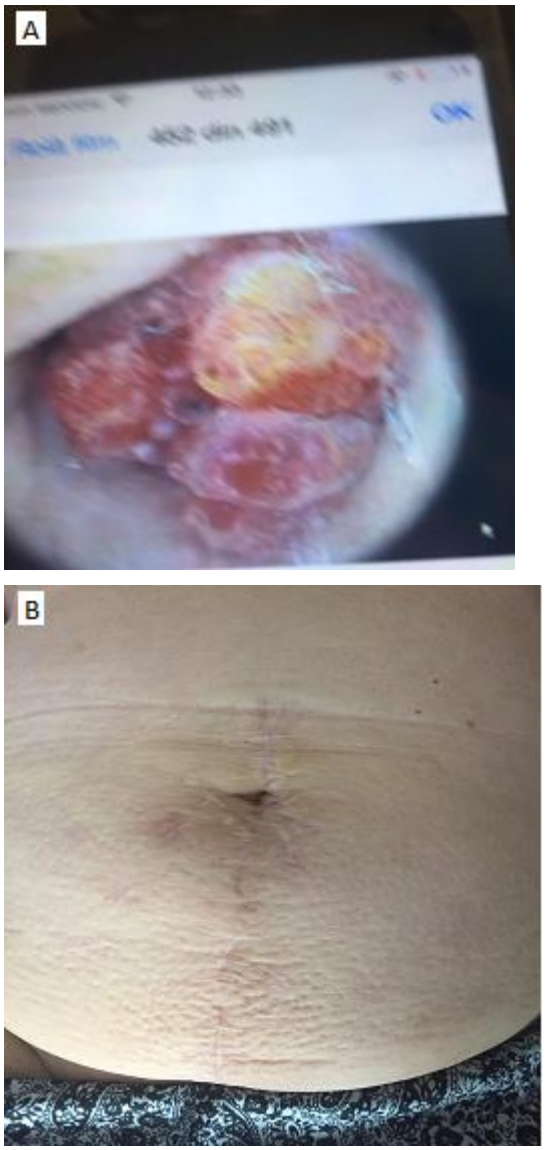

Figure 2. A: Sister Mary Joseph nodule ablated from the umbilicus. B: Abdominal skin image in March 2019.

III. *Discussion*

A. History of SMJN

The umbilical lesion known since more than 150 years as a sign of an abdominal malignancy, and named "Sister

Reference [2] cited by [3], was the first who described in 1864 the metastatic umbilical nodule and [4] (in 1949) was the first who characterized, and named this pathologic discover as "Sister Mary Joseph" nodule, after the fist description of William Mayo (1928), and after the first observations of the superintendent nurse Mary Joseph Dempsey (1856-1939), a catholic sister at Saint Mary's Hospital, Rochester (actual Mayo Clinic), Minnesota (USA). The medical literature associates the nodule to malignancies with primitive origin in the digestive (stomach, colon and appendix, gall- bladder, pancreas or pancreato-biliary tree), respiratory, urinary or genital tract – ovarian, or endometrial primitive carcinomas, or cervix uteri, very recently discovered in a North American 88 years old woman [**5**] or even peritoneum [6], and to non- Hodgkin's lymphoma in Tanzanian population [**7**].

The primary digestive origin is more frequent - 55% of cases [8], and the genitalia are in a percentage of 28% cases [9]. It is discovered in men and women, being more frequently described in women (female/male ratio, 4.1:1.0) [10]**,** from all over the world**,** from Europe, Africa, Asia (from Israel to Japan), North America**,** usually in elder patients, from the middle ages to 90's, but as the age of malignancies is descending, it was fond also in younger women, at 18 years [**10**], and with endometrial origin at the age of 30, in a Japanese women [11]. In 1996 the French physicians [12] described 27 cases of SMJN with endometrial carcinoma as primitive malignancy, and in 1998 also French physicians [13] described 368 cases of SMJN during 1960 and 1995, of which 41.3% were discovered prior to the primary tumor diagnosis, like in the Romanian case. The medical literature of different languages describes 33 cases with endometrial carcinoma and SMJN, the Romanian case being the 34th. SMJN is traditionally considered a sign of an advanced primary malignancy, and it is associated to a poor prognosis; the average survival time being reported to be 11 months, and less than 15% of the patients surviving over 2 years [14]. SMJN may be discovered also in the conditions of a malignancy recurrence [8], being described a North American man with SMJN after 5 years from an appendicular mucinous adenocarcinoma treated wirh surgery and intraperitoneal chemotherapy [15], and a case of a Bulgarian women with SMJN after 12 years from an endometrial carcinoma surgery [16].

The SMJN may be associated to a primary cancer with unknown origin in 15- 29% cases [17], but at Duke University (USA) during 1988 to 2011, a percentage of 59% from 77 cases of SMJN are cited without the discovery of the primary tumor. [10]. Aggressive therapy – cytoreductive surgery combined with chemotherapy [8], paclitaxel, carboplatin, and bevacizumab being cited with better results [18] and/or radiotherapy according to the peculiarities of primitive malignancy [3] may increase patients' survival, Recently, in USA, at University of California, San Diego and Texas School of Medicine it is cited a two-year survival rate of only 13.5 percent regardless the etiology of the primary cancer [15].

B. Positive and Differential Diagnosis

The discovery of a SMJN imposes to think first to a metastasis, and secondary to primitive umbilical lesions, like the benign ones, which are called "Pseudo Sister Joseph Nodule**"** [19], such as omphalomesenteric duct, umbilical hernia, granuloma, omphalitis and abscess, mycosis, and eczema, or keloid scars [20]. Malignant melanoma was the most common primary umbilical malignancy in the cases from the Duke University , USA [10]. On must think that some of these pathological conditions may hide an

abdominal malignancy, being discovered that an umbilical hernia was associated to endometrial carcinomas [1, 11, 16].

a) Physical Examination

The umbilical skin may be normal or erythematous [21], or on may discover cutaneous changes as individual or grouped nodules, papules, teleangiectasis, alopecia in men, and hyperkeratotic plaques [22], and sometimes ulcerations [18], with purulent, serous, or bloody exudates. The palpation may reveal an umbilical mass of 3 to 10 cm, painful, firm or soft, or a diffuse subcutaneous induration, which can be associated to peritoneal carcinomatosis, which worsens the outcome [17].

b) Imagistic studies

Imagistic studies are mandatory for primary tumor depiction and for umbilical metastasis.

Ultrasonography may reveal a solid hyperechoic mass in the umbilicus with irregular margins, and without any signs of inflammation involving the adjacent tissue might suggest the diagnosis of a SMJN [21].

c) Cytology

The cytology obtained by fine needle aspiration or by core biopsy, which are considered simple, fast, accurate and inexpensive diagnosis tools [23; 24] or the microscopy of the tissue obtained by excision of umbilical tumor or periumbilical mass – as in the reported case, associated to immunohistochemistry may sustain the the malignancy of primary organ, being recognized 12% to be primary umbilical lesions, and the remaining being metastases [10], and all are described for differential diagnosis.

d) Histopathology

A metastatic umbilical tumor usually reveals an adenocarcinoma, but sarcomas, mesotheliomas, and melanomas have also been reported. The final diagnosis is a stage IV malignancy .

The most recent discussion of the International Society of Gynecological Pathologists [25] regarding the endometrium describes low grade and high grade endometrial cancers, according to molecular analysis:

- low grade or type 1 or endometrioid endometrial carcinoma, or the “indolent” cancer, which is estrogen dependent, has “atypical endometrial hyperplasia”, as precursor (23% cases progress to endometrioid adenocarcinoma), a monoclonal lesion, with microsatellite instability, and *ras* and *PTEN* mutations [26, 27, 28], and PTEN gene loss in up to 65% cases with Endometrial Intraepithelial Neoplasia (EIN) and in 85% cases with endometrioid carcinoma [29] with estrogen and progesterone receptors at immuno-histochemistry analysis [30], discovered more frequent in white, Caucasian women, and younger women. This type of endometrioid endometrial carcinoma was complicated by SMJN after 12 years in the Bulgarian case [16].

- high grade endometrial carcinomas are represented by previous FIGO grade 3 endometrioid carcinoma, serous endometrial carcinoma, clear cells endometrial carcinoma, undifferentiated carcinoma, and carcinosarcoma. They are non-estrogen dependent, more aggressive, with atrophia or with a polyp rather than hyperplasia as precursor, and they are nonresponsive to progestins [31]. They contain *p53* mutations and abnormal accumulation of p53 protein, and absence of ERs, PRs [30, 32]. The literature presents the majority of cases of SMJN to be associated to high grade endometrial carcinomas, the Romanian case may be considered a high grade endometrial carcinoma, because the serous component .

C. Mechanisms of tumor dissemination to the umbilicus

The mechanisms of tumor dissemination to the umbilicus are poorly understand, being proposed since long time some routes for the spread of the malignant cells in conjunction to the special and unique place of the umbilical skin and the periumbilical areas- the proximity of the abdominal and pelvic organs [10, 22]. There are discussed as possible mechanisms of dissemination:

- direct or contiguous transperitoneal spread *via* the lymph vessels along obliterated umbilical vein, or

- hematogenic dissemination through access to venous or arterial channels of the anterior abdominal wall, which vary by patient anatomic peculiarities

- *via* embryologic remnants in the abdominal wall as falciform ligament, or median umbilical ligament, or a remnant of the umbilical channel

After umbilical metastases on may discover superficial axillary, and inguinal nodes, and deep para-aortic, internal mammary nodes involvement, which is explained in connection to the central point of intersections at umbilical level of the deep and superficial lymph system [13].

The parietal and umbilical invasion in the Romanian patient are through vascular spread, being discovered vascular neoplastic thrombus in the uterus and in SMJN (Fig. 1, C and D), and also positive left external iliac nodes.

IV. *Conclusions*

SMJN is a cutaneous metastasis in which the metastatic tumor presents as an umbilical mass, being more frequent in women, and in elder patients on must think first at a metastasis from an abdominal organ, the endometrium being the last after the first two locations the biliopancreatic tree, and the ovary, but there are populational/rasial variations. The sonography, MRI and molecular markers are useful tools of the diagnosis, but the golden standard is the pathological diagnosis of the primary tumor. The Romanian reported SMJN was associated to a medium and weak differentiated endometrioid endometrial carcinoma with squamous component and desmoplazic reaction, a high grade type of endometrial malignancy, diagnosis which was not suggested by the biopsy of the SMJN.

The complex and aggressive therapy may improve the patient outcome, if on consider the immuno histochemistry of the primary tumor and its metastasis, and the long duration from the appearance of the cutaneous umbilical mass, and the moment of surgery, radiotherapy and hormone therapy.

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CONFLICT OF INTEREST

The authors have no conflict of interest to disclose.

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