Heterologeous mullerian mixed tumor after whole body irradiation because of Hodgkin's disease in stage IV

R. Meyberg, C. Villena-Heinsen, R. Axt, W. Schmidt, M. Friedrich

Department of Gynecology and Obstetrics, University of Homburg/Saar (Germany)

Summary

Purpose: With an incidence of 1.5% of all malignant diseases of the uterus as specified in the literature, the mullerian mixed tumor is a rarity amongst the malignancies of the female genital tract.

Methods: A retrospective analysis of an individual case report with the occurrence of heterologous mullerian mixed tumor years after irradiation because of Hodgkin's disease.

Results: This case reports describes the occurrence of a mullerian mixed tumor 12 years after the treatment of Hodgkin's disease by whole body irradiation. To our knowledge, the incidence of a mullerian mixed tumor after the treatment of Hodgkin's disease has rarely been described up to now in the literature.

Conclusion: This case report appears to indicate the possible carcinogenic potency of radiotherapy when administered many years before. A causal connection between the administration of whole body irradiation and the development of a mullerian mixed tumor cannot be established.

Key words: Heterologous mullerian mixed tumor; Irradiation; Hodgkin's disease.

Introduction

With an incidence of 1.5% of all malignant diseases of the uterus specified in the literature [1] the mullerian mixed tumor is a rarity amongst the malignancies of the female genital tract. It consists of both epithelial and of stromal components [2]. Mostly, these are polypoid bulky tumors which fill the uterine cavity and infiltrate the myometrium at an early stage. Primary locations may be the endometrium, the cervix and the ovary. In recent years, many studies have been published on the carcinogenic potency of radiotherapy which is used for therapy of Hodgkin's disease, for example in stage IV. The present case report is that of a 78-year-old woman who developed a mullerian mixed tumor after irradiation because of Hodgkin's disease 12 years before.

Case report

A 78-year-old patient was admitted to hospital with the histological diagnosis of a carcinosarcoma of the uterus. The patient had been complaining for the last three months about postmenopausal hemorrhage. An increase in the circumference of her abdomen or pain were not mentioned. She had repeatedly refused a cancer preventive examination since 1991. Menarche had occurred in the 12th year of life and menopause in the 58th year of life. Spontaneous delivery occurred twice.

Worth mentioning in the history is the whole body irradiation (dosage: 55 Gy) in the year 1982 because of Hodgkin's disease of the nodular sclerosant type in stage IV. Simultanously, chemotherapy was performed with 6 cycles of vincristin, endoxane and prednisone (De Vita scheme).

At the initial inpatient admission, the patient was in a moderately good general condition. The gynecological investigation showed a tumor extending to the navel which could not be delimited from the uterus. The rectal mucosa was smooth and sliding, the remaining abdomen was soft and the kidney beds on both sides were free. The inguinal fossae were clinically normal.

Preoperative diagnostics, the tumor markers CEA, CA 12-5 and CA 72-4 were markedly raised. CA 15-3 was in the normal range. In vaginal sonography, a space occupation with cystic-papillary structures was visible in the region. In the abdominal CT, a large partially cystic and partially solid space occupation was shown in the lower abdomen: this displaced both ureters laterally. Enlarged lymph nodes could not be detected. Furthermore, there was a sigmoid diverticulosis. In the i.v. pyelogram, there was symmetrical compression of both ureters where they entered the pelvis with slight congestion on both sides and deformation of the urinary bladder. At coloscopy, a displacement of the sigmoid in the distal descending colon as well as diverticulosis without indication of stenoses were detected. Intestinal infiltration could not be demonstrated. Further preoperative diagnostics were normal.

With the histological diagnosis of a carcinosarcoma of the uterus, exploratory laparotomy with abdominal hysterectomy, bilateral adnexectomy, pelvic lymph node sampling and appendectomy were performed. Intraoperatively, a tumor extending to the navel and originating from the uterus with a smooth surface on all sides was shown. There was no ascites. A peritoneal carcinosis was not found. Postoperatively, the patient received no percutaneous irradiation of the pelvic region because of previous irradiation for Hodgkin's disease.

In the follow-up examination three months after discharge, the patient complained of a therapy resistant lymphocele. Therefore a laparotomy was performed. Intraoperatively a 4 cm large infiltration of the omentum minus was seen and excised; it was histologically diagnosed as a modestly differentiated, partly papillary adenocarcinoma according to a metastasis of the epithelial component of the herologous mixed mullerian tumour. Systemic therapy with medroxyprogesterone acetat (500 mg/die) was started. Further clinical and diagnostic investigation did not reveal any indication of recurrence.

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One and a half years after primary diagnosis, the abdominal CT showed tumorous lesions in the entire lower abdomen with distinct ubiquitous thickening of the peritoneum and severe ascites. An exploratory laparotomy was performed. Intraoperatively, a carcinosis of the peritoneum was seen that could not be removed surgically. Because of the intraabdominal tumor progression, further palliative chemotherapy was started with taxol (90mg/m^2) and cisplatin (40mg/m^2) weekly. After three cycles chemotherapy was changed to taxol (90mg/m^2) and carboplatin (200mg/m^2) weekly because of reduced renal function. After four cycles the patient revealed paralysis and paraesthesis. Therefore chemotherapy was switched to gemcitabine (1000mg/m^2). Two and a half years after primary diagnosis of a heterologous mullerian mixed tumour, the patient died of a protracted multiorgan failure because of rapidly progressive tumour disease.

Histology

In the histological investigation, a mullerian mixed tumor was diagnosed. The final histological workup revealed an extensive necrotic biphasic tumor consisting of solid epithelial formations with focal squamous epithelial differentiation, in part with epithelial pearl formation. Besides this, immature tubular glandular structures could be detected. The stroma had a dense cellular structure and contained partially focal chondroid differentiated parts. Numerous vascular infiltrations could be detected. The tumor infiltrated the myometrium, where it extended almost up to the serosa. The remaining corpus mucosa which was still intact showed polypoid protuberances in places and was cystically atrophic. Estrogen and progesterone receptors were demonstrable immunohistochemically only in sarcomatous components. Both adnexae, the vermiform appendix and the exploratory peritoneal excisions were free of tumor. In the pelvic lymph nodes no tumorous infiltrations were shown.

The histological finding was thus a mullerian mixed tumor of heterologous type of the corpus uteri with lymphangiosis and hemangiosis but no lymph node metastases. The tumor stage was classified with pT 1b, pN 0, the grading with G3 analogous to the classification of endometrial carcinomas. The prognosis was regarded as poor because of the high grading, the undifferentiated epithelial parts with a high number of mitosis and severe nuclear polymorphism.

Discussion

Amongst the endometrial malignancies which have arisen under radiotherapy, a relatively high percentage of sarcoma is found, e.g. adenosarcomas, homologous and heterologous mullerian mixed tumors [3].

Mixed epithelial, non-epithelial tumors of the uterus are classified as follows [4]:

1. benign:
   - adenofibromas
   - adenomyomas
2. malignant:
   - adenocarcinomas
     > homologous
     > heterologous
   - carcinosarcomas (malignant mullerian mixed tumors)
     > homologous
     > heterologous
   - carcinofibromas

Histologically, malignant mesodermal mixed tumors comprise a sarcomatous and a carcinomatous part. In homologous forms, the sarcomatous component is undifferentiated. The prognosis of the heterologous forms is regarded as particularly poor. They contain one or several sarcomatous components, e.g. with chondroblastic, rhabdomyoblastic or osteoblastic differentiation. The metastatic spreading takes place via the regional lymph nodes: one fifth of the patients show metastases in the pelvic lymph nodes at the time of the operation [4].

Carcinosarcomas are probably subject to a hormonal effect [5]. Estrogen receptors could be detected not only in the epithelial endometrial glands but also in the sarcomatous portions. Press and Scully *et al.* [6] reported on six patients who developed adenosarcomas under the influence of estrogen. Alteras *et al.* [7] observed two cases with adenosarcoma under estrogen therapy on its own. Histologically, most endometrial malignancies under tamoxifen therapy are adenocarcinomas [8]. Stewart and Knight *et al.* [9] referred to three adenocarcinomas in 539 patients under adjuvant tamoxifen therapy, whereas of 531 patients in the untreated control group no patient developed an adenosarcoma. In view of the low incidence of all sarcomas of the uterus with 1.7 per 100,000 women, the incidence of adenosarcomas of 1:180 in the group treated with tamoxifen indicates a distinctly raised risk [3, 10]. On the other hand, according to Barakat *et al.* [10], there do not appear to be any significant differences with regard to the stage, grading and histological character of the endometrial malignancies under tamoxifen therapy. This is also apparent in the NSABP Study by Fischer *et al.* [11]. However, Margriples *et al.* [12] report that there was a significant difference in the histological character of the corpus mali-

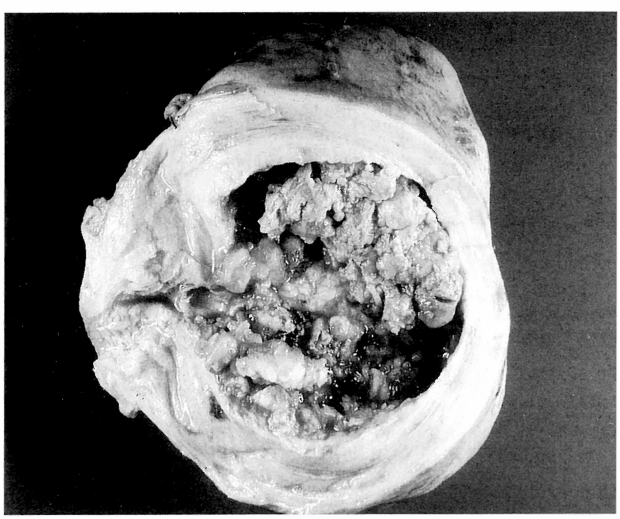

Figure 1. — Surgical preparation of a mullerian mixed tumor with intracavity tumor growth.

Table 1. — *Cancers subsequent to irradiation for benign conditions.*

Author	Corscaden [18]	Costolow [19]	Crossen [20]	Montgomery [21]	Hunter [22]	Palmer [17]
No. of patients	958	1,009	526	831	644	721
Followed less than 10 years	78%	not stated	not stated	76.8%	65%	0
Subsequent cancer						
Corpus	9	3	4	9	2	29
Cervix	6	2		2		11
Ovary	2	1	1	1	1	8
Total	17 (1.78%)	6 (0.59%)	5 (0.95%)	12 (1.41%)	3 (0.46%)	48 (6.65%)

gnancies of the two groups with 67% little-differentiated endometrial malignancies in the group treated with tamoxifen (mainly 40 mg tamoxifen per day) as compared to 24% in the untreated group. van Leeuwen [13] found highly differentiated endometrial malignancies in 52% of the tamoxifen-treated group as compared to 32% in the untreated group in a study comprising 382 patients.

An increased risk of cancer of the corpus uteri after radiotherapeutic castration and treatment for benign pelvic disorders with intracavity radium or external X-rays has been reported. Brinkley *et al.* [14] in their study on the late effects of artificial menopause by X-radiation described a significantly increased mortality from all causes, an increase of mortality that is mainly attributable to an increase of deaths from cancer of heavily irradiated sites occurring more than five years after irradiation and a significant increase in the total number of deaths within five years of treatment which is mainly attributable to deaths from coronary disease, myocardial degeneration and cerebrovascular disease. Doll *et al.* [15] published the results of a follow-up of 2,068 patients treated with X-rays for metrophathia haemorrhagica and found that five or more years after treatment there was an increased mortality in the treated group from leukaemia and from cancer at sites within the irradiated area. Hardell [16] described an increased risk of uterine cancer in respect to both radiotherapy and tamoxifen treatment. The oestrogen-like stimulating effect on endometrium by tamoxifen seems to be a risk factor in the absence of irradiation. Radiotherapy may have an initiating effect and tamoxifen a hormonal, promoting effect in the causation of uterine cancer. Palmer *et al.* [17] found the ratio of cancer after radiotherapy compared to those expected to be high in every part irradiated, ranging from a low ratio of 1.531:1 for the cervix to 5.95:1 for the corpus to the highest ratio of 11.78:1 for the vagina. Concerning the malignancies of the corpus uteri they did not find any sarcomas.

Table 1 lists the number of cancers of the corpus, cervix and ovaries occurring subsequently to irradiation for benign conditions.

Nevertheless, a causal correlation between radiotherapy and the development of a mullerian mixed tumor cannot be established. Only large-scale, well-run epidemiological studies can contribute to establishing the risk of the development of a second carcinoma after irradiation, taking into consideration the different therapy parameters (dosage, duration of therapy).

Even if radiotherapy for Hodgkin's disease at a conventional dosage (55 Gy) clearly increased the incidence of uterine malignancies (carcinomas, sarcomas, carcinosarcomas), the benefits predominate. The global benefit of adjuvant radiotherapy must be considered not only with regard to the reduction in the risk of progression or recurrences, but also the increase in the length of the recurrence-free interval and the overall survival. Many women benefit in terms of a lowering of the rate of recurrences, whereas only a few suffer from a second malignancy after irradiation. Our efforts should be focused on adequate endometrial and uterine monitoring after radiotherapy.

Conclusion

The incidence of heterologous mullerian mixed tumor after whole body irradiation for Hodgkin's disease appears to be an indication for the possible carcinogenic potency of radiotherapy.

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Address reprint requests to:
MICHAEL FRIEDRICH, M.D.
Universitäts-Frauenklinik mit Poliklinik
und Hebammenlehranstalt
Universität des Saarlandes
D-66421 Homburg/Saar (Germany)