Metastatic spread of gynaecological neoplasms to the adrenal gland: case reports with a review of the literature

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Summary

Metastatic involvement of the adrenal glands due to gynaecological neoplasms is a relatively rare condition. The aim of our study was to present four cases of metastases to the adrenal gland due to endometrial adenocarcinoma, ovarian and cervical cancer. These cases are correlated with a review of the literature. CT scan and MRI have been previously used in an attempt to define the nature of the adrenal mass but this approach is of limited value in diagnosis. Image-guided pathological confirmation of an adrenal lesion may significantly change the staging or management of the primary neoplasm. The authors suggest that isolated adrenal metastasis should be routinely considered for surgical management.

Key words: Adrenal metastasis; Endometrial adenocarcinoma; Ovarian cancer; Cervical cancer; Vulvar cancer.

Introduction

The most common tumours to metastasise to the adrenal gland, in order of frequency, are lung cancer, breast cancer, gastrointestinal tumours, followed by malignant melanoma and thyroid neoplasms [1]. The metastatic involvement of the adrenal glands due to gynaecologic neoplasms is a relatively rare condition. Autopsy reports indicate an incidence of 25% for all malignancies [2]. However, the clinically antemortem observed ranges are difficult to estimate.

The aim of our study was to present four cases of metastases to the adrenal gland due to gynaecological neoplasms and to correlate our findings with a review of the literature.

Clinical and pathologic factors were assessed in four patients with a metastasis of the adrenal gland from primitive gynaecological cancer.

In addition, we reviewed the English literature using PubMed over the past 30 years using the following key words: “adrenal metastasis”, “endometrial adenocarcinoma”, “ovarian cancer”, “cervical cancer”, “vulvar cancer”. We present the most representative cases reported.

Case Reports

Case 1

A 76-year-old woman was referred to our cancer centre with a diagnosis of FIGO Stage IV endometrial carcinoma in 1996. Pathological right acetabular fracture and bone biopsy suggested the diagnosis.

The patient underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy and pelvic lymph node dissection. Histopathological results revealed an endometrial adenocarcinoma, well differentiated, with depth of myometrial invasion in the inner one-third, with no invasion of the cervix or adnexa and no pelvic node involvement. The patient underwent postoperative pelvic radiation (40 Gy) with a booster dose on the right ischiopubic bone.

The patient was asymptomatic and physical examination was normal. Surveillance computed tomography (CT) scan performed nine months later showed a 50 mm suspicious right adrenal mass. Laparotomy was performed and only partial resection was carried out due to the direct extension to adjacent organs (liver, inferior cavous vein). Pathological examination was consistent with a metastasis of an endometrial adenocarcinoma. The patient was administered medroxyprogesterone (500 mg per os daily). She subsequently developed recurrence with lung metastases and died two years after initial surgery.

Case 2

A 62-year-old woman, gravida 2, para 2, presented in 1992 with postmenopausal bleeding. She underwent a hysteroscopy which revealed an irregular endometrium. A biopsy during the procedure revealed a well differentiated endometrial adenocarcinoma. CT scan of the abdomen and pelvis was considered normal. After uterovaginal brachytherapy (60 Gy), the patient underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy and pelvic lymph node dissection. Histopathology revealed no residual tumour and 15 pelvic lymph nodes without metastases.

At follow-up seven years after initial surgery, the patient presented with dyspnea. Lung metastases from endometrial carcinoma were detected on the chest CT scan, and confirmed by bronchoscopy and biopsies, with no other evidence of disease. The patient received six courses of adriamycin and cisplatin. She also underwent a second-line treatment with medroxyprogesterone (500 mg per os daily). After a two year period of remission, she was admitted due to dyspnea. CT revealed marked disease recurrence with lung metastases and bilateral inhomogeneous solid masses of the adrenal glands (right 40 x 18 mm, left 44 x 21 mm) as well as a collection of ascites resembling peritoneal carcinosis. The patient was treated with analgesic medication and died two months later, nine years after the initial diagnosis.

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Table 1. — *Summary of reports on metastases of the adrenal gland from primitive gynaecologic cancers.*

Authors	Ref	Number	Histology report
Gross BH	[3]	1	Vulva, squamous cell carcinoma
Redman BG	[12]	1	Ovary, no details
Drescher CW	[8]	7	Uterine cervix, adenocarcinoma
Nakano KK	[13]	1	Uterus, clear cell adenocarcinoma
Patlas M	[11]	1	Ovary, serous adenocarcinoma
Einat S	[10]	1	Ovary, papillary adenocarcinoma

Case 3

A 62-year-old woman was admitted to our cancer centre in 1997 due to abdominal pain and swelling. On physical examination an abdominal mass was found. Ultrasound and CT scan of the abdomen and pelvis revealed a heterogeneous pelvic mass, which developed from the right ovary. CT scan showed a right upper lobar bronchus mass and three suspicious brain lesions. A bronchoscopy with biopsies confirmed the diagnosis of metastasis due to ovarian cancer. The patient underwent a total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and appendicectomy. During the procedure, a left adrenal mass was removed. Pathological examination revealed a bilateral, poorly differentiated, papillary ovarian adenocarcinoma.

The patient was subsequently treated with a combination of cyclophosphamide and paraplatine, and whole brain radiotherapy. The patient died six months later.

Case 4

In 1996, a 61-year-old woman gravida 7, para 7, with a previous history of subtotal hysterectomy for adenomyosis, presented with squamous cell carcinoma of the cervix. The lesion was Stage FIGO IB1 based on physical examination including the chest X-ray, abdomen and pelvic CT scan as well as cystoscopy.

The patient underwent an abdominal radical cervicectomy and pelvic lymph node dissection. Histopathology revealed a 20 x 15 mm well differentiated squamous cell carcinoma with vascular lymph space invasion and healthy margins, and 19 pelvic lymph nodes without metastases. Postoperative pelvic radiation was subsequently administered (48 Gy).

Surveillance CT performed six months after initial surgery showed a new 27 x 20 mm nodule in the left adrenal gland. A CT scan obtained six months later showed that the adrenal nodule had increased in size to 50 x 40 mm. Laparatomy was performed to remove the mass. Pathological findings revealed a mass completely surrounded by the adrenal capsule, consistent with a metastasis of squamous cell carcinoma. A period of watchful waiting was decided and six months after the left adrenalectomy, a CT scan confirmed a solitary right adrenal mass (25 x 15 mm). There were no other sites of metastatic spread, and a right adrenalectomy was performed by laparotomy, confirming the second metastasis of the cervix neoplasm.

Six months later, due to the evidence of recurrent disease (lomboaortic and mediastinal lymph node enlargement), the patient received six courses of mitomycine (day 1, 6 mg/m^2) etoposide (days 1-3, 100 mg/m^2 a day) bleomycine (days 1-3, 10 mg/m^2 a day) and cisplatinum (day 4, 80 mg/m^2). Partial regression of the tumoral mass was observed on follow-up CT scan.

The patient died two years after initial diagnosis.

Discussion

We report two cases of metachronous metastases to the adrenal gland from endometrial adenocarcinomas (cases 1 and 2) and two cases of synchronous metastases from ovarian cancer (case 3) and from cervical cancer (case 4). As a short disease-free interval (≤ 6 months) is an indicator of biological aggressiveness of the tumour, we considered case 4, where the adrenal metastasis was discovered within six months of diagnosis of the primary tumour, as M1 (synchronous). All cases, except case 2, were metastases confirmed by surgical pathology evaluation.

Most asymptomatic adrenal lesions are found on CT scan, with a high degree of accuracy in detecting adrenal masses as small as 5 mm [3, 4]. An incidentally discovered adrenal mass, in a patient with no previous history of cancer, is rarely malignant or metastatic, corresponding to a benign non-functioning nodule (including nodular hyperplasia and adenoma). In contrast, as many as 36% of adrenal masses in patients with a history of malignant disease are metastatic [2]. This suggests that over 50% of adrenal masses are benign [4]. All patients had a previous medical history of malignancy and all were asymptomatic (i.e. without clinically apparent adrenal disease). Symptoms such as asthenia, lassitude, weight loss or nausea are common in patients with widespread malignancy and were absent in all cases. Seidenwurm *et al.* recommend that any patient found to have enlarged adrenal glands on CT scan and known cancer, should undergo endocrine testing to detect adrenal insufficiency by an ACTH stimulation test [5].

Various imaging techniques have previously been employed in an attempt to define the nature of the adrenal mass. CT scan cannot reliably characterise an adrenal lesion as benign or metastatic. Size above 50 mm, invasion into adjacent tissue, and a growing mass at follow-up CT scan are helpful criteria in distinguishing malignant lesions from adenomas. Attenuation values of less than 10 Hounsfield units at unenhanced CT are practically diagnostic for adenomas, while attenuation values of greater than 10 HU are not diagnostic of metastatic disease since non-metastatic disease is also a possibility. Magnetic resonance imaging (MRI) is of limited value. Nevertheless, an adrenal lesion with decreased signal intensity in out-of-phase MRI acquisition may be regarded as benign [18]. F-FDG PET could possibly be useful in differentiating benign from metastatic adrenal lesions detected on CT or MRI, with a sensitivity of 100%, a specificity of 94%, and an accuracy of 96% (patients with lung cancer). In addition, PET scan has the advantage of revealing the primary cancer sites and detecting other metastases.

Pathological confirmation of an adrenal lesion is of prime importance for subsequent management [4, 7]. Although percutaneous fine-needle aspirations or core biopsies are sensitive, specific and less invasive techniques than surgery, we decided to perform three laparotomies for two patients in order to assess the diagnosis (cases 1 and 4). For case 3, the adrenal metastasis was diagnosed during the surgical debulking procedure of an

ovarian cancer. Complete resection rendering the patient free of disease was possible in only one case (case 4), for a two-stage procedure with an interval of six months. No major perioperative complications were found. With evidence of metastatic disease (brain, lungs), case 3 should not have been selected for surgical management.

Patients whose adrenal metastases are discovered synchronously may be less amenable to cure from metastasectomy because other "occult" sites may rapidly be revealed after surgery. According to Kim *et al.*, adrenalectomy should be strongly considered for surgical management if complete resection of an isolated metastasis can be achieved, given the relatively poor results reported with radiation and chemotherapy. A disease-free interval > 6 months is a significant predictor of improved survival [1, 8]. Adrenalectomy can be performed safely and could prolong survival in selected patients. The oncological outcome appears similar with no difference in the incidence of positive resection-margins or survival between patients with laparoscopic adrenalectomy or open adrenalectomy [8].

Cervical carcinoma

In a retrospective review of autopsy findings and comparison of the pattern of metastatic spread of squamous cell carcinoma and adenocarcinoma of the cervix, adrenal gland involvement was observed in seven of 21 patients with adenocarcinoma and in none of 21 patients with squamous cell carcinoma. This may indicate a propensity toward hematogenous spread, possibly along the ovarian vessels. Additionally, the adrenal gland may provide a local hormonal factor that is favourable for the growth of metastatic implants in adenocarcinoma. [9]. To our knowledge, we report the first case (case 4) of bilateral adrenal metastasis from squamous cell carcinoma of the cervix. Gross *et al.* previously reported this type of histological lesion from a vulvar carcinoma [3].

Ovarian carcinoma

Ovarian carcinoma can spread via peritoneal implantation, lymphatic invasion, and haematogenous dissemination. Hematogenous metastases from ovarian carcinoma may become more commonly recognised as new treatments are implemented, resulting in improved survival rates. The reported prevalence of adrenal metastases in patients with ovarian cancer at autopsy is 15% [10]. Einat *et al.* reported the case of successful laparoscopic removal of a solitary adrenal metastasis from an ovarian papillary adenocarcinoma [11]. The patient was clinically free of disease after two years of follow-up. A case of simultaneous adrenal and pancreatic metastases in a patient with serous ovarian carcinoma has also been reported, with no further treatment following the diagnosis of metastasis [12]. The third case was a CT scan description of a bilateral adrenal gland enlargement consistent with metastatic disease from an ovarian carcinoma in a prospective evaluation of adrenal insufficiency in 15 consecutive patients with adrenal metastasis [13]. No data are available on histology, adrenal insufficiency, treatment or follow-up for this particular patient. According to these authors, one third of the patients in this series presented with an adrenal insufficiency.

Endometrial carcinoma

The sole reported case of adrenal metastasis from endometrial carcinoma was an advanced stage of a particular subtype [14]. Clear-cell carcinoma of the endometrium is a highly malignant neoplasm that accounts for less than 5% of endometrial carcinomas. Cases 1 and 2 were more common and well differentiated endometrial carcinomas, nevertheless these patients subsequently experienced widespread malignancy after a disease-free interval of nine months and seven years. In case 1, an approach other than an "aggressive" and incomplete surgery should have been considered due to an initial Stage IV synchronous bone metastasis.

Conclusion

An incidentally discovered adrenal mass in a patient with a history of cancer should suggest histological confirmation, which avoids a mistaken diagnosis of metastasis in patients with benign adrenal masses or detects an unusual adrenal metastasis. Adrenal metastasis most commonly occurs due to multiple synchronous metastases in other sites. Palliative management is then considered the treatment option. Resection of solitary adrenal metastasis may offer the best alternative to cure the patient and can be achieved both by laparoscopy or laparotomy.

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