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Original Research Article

Multiple Neoplasms in the Female Genital Tract

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Abstract

Context: Hysterectomy is one of the most common gynecological surgeries performed. Neoplastic lesions form an important indication for hysterectomy. Histopathological analysis of these specimens adds valuable information and at times reveals multiple neoplasms affecting the female genital tract.

Aims: To determine the prevalence of multiple primary neoplasms in the hysterectomy specimens

Methods and Material: All the hysterectomy specimens with or without adnexectomy in a 2 year period were studied for their histomorphological features and multiple neoplasms thus noted were recorded.

Results: A total of 510 hysterectomies were analyzed. Twenty one cases had multiple neoplastic and/or pre neoplastic lesions in the female genital tract.

Conclusions: Though multiple neoplasms occurring in the female genital tract are rare, longer follow up in cancer survivors will throw more light on the prevalence and prognosis of such lesions.

Keywords: Neoplasms; Multiple Primary; Hysterectomy; Uterus.

Introduction

Throughout the ages the uterus has been given a very special status because of its function in the beginning of all human life. The female reproductive tract is constantly harassed by diverse conditions like pelvic inflammatory diseases, menstrual disorders to neoplasms forcing the patients to seek gynaecologists help. Although medical therapy is available for many of these, surgical intervention is done in the form of hysterectomy.

The development of satisfactory surgical technique that permits removal of the whole uterus without increasing the mortality and morbidity, that preserves the normal anatomical features of the vaginal vault has led to increase in number of hysterectomies as choice of operation for a variety of clinical conditions.

Multiple primary neoplasms in a single patient have been well documented in literature over the past century. The lesions can be limited to the single or may involve multiple organ systems. The reported frequency of multiple primary cancers (MPC) varies in different studies. The interesting occurrence of multiple neoplasms and pre neoplastic conditions in such a scenario prompted us to undertake the study to determine their prevalence in hysterectomy specimens.

Materials and Methods

This was a histomorphological study undertaken in the Department of Pathology in a medical college catering to predominantly rural population over a period of 2 years from July 2009 to June 2011.

All the hysterectomy specimens with or without adnexectomy received during this period were studied for their histomorphological features. The specimens were fixed in 10% neutral buffered formalin and relevant sections were taken according to protocol for histomorphological evaluation.

Paraffin embedded sections derived from these bits were stained with hematoxylin and eosin and studied microscopically.

Cervical and endometrial biopsies, oophorectomy specimens and myomectomy specimens were excluded from the study.

Results

A total of 4219 surgical biopsy specimens were received for histopathological evaluation during the study period July 2009 to June 2011. Of these, the number of hysterectomy specimens was 510. This constituted 12.08% of all the biopsy specimens received.

Of the hysterectomies performed, the table 1 shows the number of cases in which additionally the adnexae were also surgically excised with the uterus.

Out of 510 hysterectomy cases studied, 210 cases showed neoplasms of which 189 cases had single lesion and 21 cases showed multiple lesions.

An interesting observation of this study was the existence of multiple neoplastic and pre-neoplastic conditions within a given hysterectomy specimen. A total of 21 such multiple neoplastic lesions were encountered.

Table 1: Status of removal of adnexae in hysterectomy

Status of adnexal removal	Number of cases	Percentage
Unilateral salpingo oophorectomy	38	7.45
Bilateral salpingo oophorectomy	163	31.96
No adnexae removed	309	60.59

Table 2: Multiple preneoplastic and neoplastic lesions noted in hysterectomy specimens

Group 1: Cervix with ovary (2 cases)	
CIN-III	Serous cystadenoma ovary
CIN-III	Mixed germ cell tumour ovary
Group 2: Cervix with uterine myometrium (10 cases)	
CIN-II	Leiomyoma
Squamous cell carcinoma	Leiomyoma
Adenosquamous carcinoma	Leiomyomata
CIN-III	Leiomyoma
CIN-II	Leiomyoma
CIN-II	Leiomyomata
Squamous cell carcinoma	Leiomyoma
Squamous cell carcinoma	Leiomyoma
Squamous cell carcinoma	Leiomyomata
CIN-II	Leiomyoma
Group 3: Ovary with ovary(1 case)	
Serous cystadenoma right ovary	Fibrothecoma left ovary
Group 4: Uterus with ovary (6 cases)	
Leiomyoma	Papillary serous cystadenoma
Leiomyoma	Benign Cystic Teratoma
Leiomyoma	Serous borderline tumour
Leiomyoma	Benign Cystic Teratoma
Leiomyoma	Serous cystadenoma ovary
Leiomyoma	Mucinous borderline tumour
Group 5: Endometrium with myometrium (2 cases)	
Endometrial adenocarcinoma	Leiomyoma
Endometrial adenocarcinoma	Leiomyomata

CIN: Cervical Intraepithelial Neoplasia

Table 3: Biological behaviour of the cases studied

Group 1 : Benign with benign	**5 cases**
Serous cystadenoma right ovary	Fibrothecoma left ovary
Leiomyoma	Papillary serous cystadenoma
Leiomyoma	Benign cystic teratoma
Leiomyoma	Benign cystic teratoma
Leiomyoma	Serous cystadenoma ovary
Group 2: Benign with borderline	**2 cases**
Leiomyoma	Serous borderline tumour
Leiomyoma	Mucinous borderline tumour
Group 3: Premalignant with benign	**6 cases**
CIN-III	Serous cystadenoma ovary
CIN-II	Leiomyoma
CIN-III	Leiomyoma
CIN-II	Leiomyoma
CIN-II	Leiomyomata
CIN-II	Leiomyoma
Group 4: Benign with malignant	**7 cases**
Squamous cell carcinoma	Leiomyoma
Adenosquamous carcinoma	Leiomyomata
Squamous cell carcinoma	Leiomyoma
Squamous cell carcinoma	Leiomyoma
Squamous cell carcinoma	Leiomyomata
Endometrial adenocarcinoma	Leiomyoma
Endometrial adenocarcinoma	Leiomyomata
Group 5: Premalignant with malignant	**1 case**
CIN-III	Mixed germ cell tumour ovary
Group 6: Malignant with malignant	**0 case**

CIN: Cervical Intraepithelial Neoplasia

The 21 cases which showed multiple neoplastic and pre neoplastic conditions within a given hysterectomy specimen are tabulated in Table 2. As noted, the most common association was with the preneoplastic and neoplastic lesions of cervix and the uterine myometrial leiomyomas.

The same cases were analyzed for their biological behaviour and the following categories as depicted in Table 3 were arrived at.

As observed, there were no multiple primary malignancies observed in this study. A single case of cervical intra epithelial neoplasia **III** associated with a mixed germ cell tumour of the ovary was the only scenario where a premalignant lesion co existed with a malignant neoplasm.

Discussion

Multiple primary cancer (MPC) is defined as two or more cancers with no subordinate relationship occurring either simultaneously or not in the same patient [1]. The prevalence of MPC is estimated between 0.73% and 11.7% in literature [2].

Though uncommon, MPC have been reported in case reports, in clinical series and, more recently, have been quantified as incidence rates in population-based series. The proportion of MPC in clinical and autoptic series reported since 1932 ranges from 0.8% to 16%. The population-based systematic studies carried out by long standing cancer registries have reported a proportion of MPC ranging from 2.1% to 6.6% of all incident cases registered from 1935 up to 1995 [3]. The incidence of quadruple primary cancer has been reported as "<0.1% [1].

The wide variation in prevalence of MPC reported in literature could be due to several factors, such as the year and criteria of diagnosis of the MPC, the patients' characteristics (*i.e.* age, site of first primary) and the criteria of selection of cases for autopsy. Site seems to play an important role, with most MPC arising in the respiratory, gastrointestinal and genitourinary systems [3].

Spratt et al. suggested that persons living to extreme age can expect to have multiple cancers with great frequency [4]. The occurrence of MPC has risen as the cure rate and survival increase due to improvements in diagnostic techniques and treatment [1].

Previous authors have reported synchronous malignancy incidence among gynaecologic neoplasms between 0.8% and 1.7% [5]. Ayhan et al. reported that the incidence of multiple primary cancer of the female reproductive tract is 1.7%, and 51.7% of these cases occur in the endometrium and ovary [6]. Moertal et al reported that the incidence of cancer in additional organs in females with reproductive tract cancer is 2.8%, and the most frequent pairings are ovarian cancer and lung cancer, or ovarian cancer and colon cancer [7]. Synchronous cervical and endometrial cancers are even rarer [8].

In the current study there were no multiple primary malignant neoplasms. The only scenario where a potentially malignant lesion co existed with a malignancy was that of a CINIII co existing with a mixed germ cell tumour of the ovary. The benign leiomyoma frequently co existed with both cervical and endometrial malignancies. They were also noted together with borderline ovarian neoplasms. Pre malignant lesions of cervix too co existed with leiomyomas.

Cervical intraepithelial neoplasia (CIN) is the spectrum of lesion representing the precursors of cervical squamous cell carcinoma. CIN represents the pre invasive counter part of invasive cervical squamous cell carcinoma, and there is now abundant evidence for its malignant potential. However there is no inevitability about their neoplastic progression. These lesions may regress, remain phenotypically stable or progress [9-11].

Multiple primary tumours were first described by Billroth in 1889 [12]. Warren and Gates proposed three criteria for the diagnosis of a second primary cancer that are still followed by the majority of authors: each tumour should show specific malignant findings; the tumours should differ in site and one tumour should not be a metastatic focus from another [13].

Most coexistent multiple cancers are direct extensions or metastatic from one organ. However, it is imperative to distinguish metastatic disease from independently existing primary tumours, as overall survival and treatment differs considerably. Several pathologists have put forth various clinico-pathological criteria to aid clinicians and pathologists in differentiating metastatic disease from primary coexisting malignancies. These criteria include either different histological types (major criterion) or all of the following minor criteria: (1) both tumours confined to primary sites, (2) no direct extension between tumours, (3) no lymphvascular tumour emboli, (4) no or only superficial myometrial invasion and (5) distant metastasis [14].

Moertel proposed new definitions, including the term “multicentric” if tumours occurring simultaneously in the same anatomical site shared the same histology and “metachronous” if the second tumour was diagnosed more than six months after the diagnosis of the first primary [7]. Patients with two synchronous or metachronous tumours are at a higher risk at developing further malignancies. A longer follow up in such patients will provide additional data [2].

There are multiple reports published in literature which discuss about MPC in various organ systems in general and female genital tract in particular.

Report of case of metachronous bilateral breast carcinoma with subsequent development of oesophageal cancer and endometrial adenocarcinoma has been published by Angurana et al [15]. Synchronous dual malignancy in a 70 years old female with an infiltrating duct carcinoma and large cell non keratinizing squamous cell carcinoma cervix has been reported [16].

The reported incidence of cervical carcinoma associated with ovarian adenocarcinoma is only 4%. Ostrowski has reported primary malignancy of ovary, cervix, endometrium, urinary bladder and caecum in a 51 year old female [17]. Another case of adenoacanthoma of cervix associated with adenocarcinoma of ovary, breast, bile duct and colon has been reported by Swaroop et al [18]. Mesmoudi et al report a case of a synchronous double malignancy in a 78 year old lady in her cervix and skin who later on was detected to also have a metastatic neuroendocrine carcinoma from an unknown primary site [2]. Two patients who survived five primary malignant neoplasms for 12 and 18 years respectively have been reported [3]. Report of quadruple cancer in a single patient including the breast, rectum, ovary, and endometrium is documented [1]. There are multiple reports described in literature describing co existence of ovarian and endometrial tumours, collision of endometrioid carcinoma and stromal sarcoma of the uterus, ovarian rhabdomyosarcoma with clear cell carcinoma of ovary, endometrial stromal nodule with papillary serous carcinoma of ovary etc [19]. A case of ovarian epithelial cancer fifteen years after a cervical carcinoma has been reported by Charak et al [20]. Kishan et al report an extremely rare case of endocervical malignant mixed Mullerian tumour (MMMT), leiomyoma uterus and bilateral fallopian tube carcinoma in a perimenopausal woman [21]. Synchronous malignancies, including three or more tumours, are extremely rare. A case of a woman with a concurrent simultaneous endometrial, ovarian and fallopian tubal carcinoma has been reported [5]. An unusual case of synchronous primary malignancies at five sites in the female genital tract has been reported [22].

The coexistence of carcinomas of the cervix and ovary has been reported to be a rare situation in gynecological practice [23]. In a study by Kaminski and Norris, the incidence of concomitant ovarian cancers (both primary and metastasis) in patients with cervical carcinoma was reported to be as high as 16% and only 9% of those cases

were primary ovarian tumours. In the same study, presence of the endometrioid type adenocarcinoma of the cervix was found to dictate the presence of the primary independent ovarian tumour [24]. Coexistence of villoglandular papillary adenocarcinoma of the cervix uteri and Brenner tumour in the right ovary has been reported [23]. In a study by Elishaev et al, it was reported that endocervical adenocarcinomas, can metastasize to the ovaries and simulate primary ovarian surface epithelial neoplasms. Therefore the authors suggest that detection of HPV DNA in these ovarian tumours should be performed to differentiate metastatic endocervical adenocarcinomas from independent primary tumours of the ovary [25]. In the current study pre malignant lesion of cervix viz., CIN co existed with both benign and malignant ovarian tumours.

Sarangthem et al report a case of primary bilateral tubal adenocarcinoma associated with uterine leiomyomas without evidence of metastasis occurring in a post menopausal women. The association of uterine leiomyomas in this case was considered to be a coincidence [26].

In the present study, leiomyomas frequently co existed with cervical premalignant lesions, with ovarian benign and borderline tumours and with malignancies of cervix and endometrium. In most of these cases, the association of leiomyomas may be co incidental. However, in the case of endometrial adenocarcinoma a common hormonal association may be possible.

The mechanism of multiple primary cancers is not fully understood. Many hypotheses have been suggested, such as family history, immunologic and genetic defects, prolonged exposure to carcinogens, radiation and chemotherapy for the primary cancer, and field cancerization. Field cancerization is a concept that was suggested by Slaughter et al. in 1953 [27]. It suggests that when the body is exposed to carcinogens, other organs besides the organ with cancer are also exposed to the carcinogen and carry a high risk of cancer. Goodall et al. hypothesized that the female upper reproductive system and the peritoneal epithelium have the same origin [28]. Laughlan et al. suggested that cancers developing in other sites originate from histologically similar epithelium. This "secondary mullerian system" concept attempts to explain the etiology of endometrial and ovarian synchronous multiple primary cancers [29].

According to the main aetiological factors, second primary neoplasms could be classified into three, not mutually exclusive categories *viz* syndromic cancer, cancer treatment related and shared exposure-related. Syndromic malignancies are characterized by inherited mutations of genes associated with an increased risk of cancer. Cancer treatment related tumours, once haematological malignancy has been excluded, are mainly represented by a slight increase in the incidence of lung cancer and sarcoma after postmastectomy radiotherapy. Furthermore, treatment with tamoxifen in breast cancer patients is associated with a two- to threefold increase in the risk of developing endometrial cancer, while adjuvant chemotherapy is not associated with any detectable increased risk of solid tumours. A common risk factor like cigarette smoking or alcohol consumption could be a factor in the simultaneous occurrence of tumours of the aerodigestive tract, bladder cancer and cervical cancer in women [3].

Ovarian and endometrial malignancies are the most commonly reported synchronous female genital tract malignancies. It is postulated that the extended Mullerian system, comprising the ovarian epithelium, fallopian tube, uterine corpus and cervix, may respond as a single morphological unit to a carcinogenic process, thus producing primary tumours at above-mentioned sites in varying combinations. Hormonal 'field effect' has also been proposed to explain the simultaneous occurrence of endometroid cancers at two or more sites in the upper female genital tract. Human papilloma virus (HPV) is strongly associated with cervical and vaginal squamous carcinoma, and in rare occurrence has been demonstrated in ovarian squamous intraepithelial neoplasia, although the association is less clear. Rare occurrences of synchronous ovarian and vaginal malignancies are reported in literature. Simultaneous occurrence of histologically distinct tumours in embryologically different sites in the female genital tract could probably be a chance occurrence [14].

Estrogenic activity in a functional ovarian tumour like thecoma has been known to be associated with endometrial hyperplasia and carcinoma. Estrogen influence on myometrium leading to from action of fibroids is debated. A case of thecoma with uterine leiomyoma coexisting in a menopausal woman has been reported by Sane [30].

Conclusion

While multiple neoplasms in the female genital tract may present themselves are diagnostic rarities, devising treatment protocols in such cases will always be a challenge. There are no established therapeutic rules for multiple primary cancers, but the type, progression, response to therapy, and patient's general health status should be considered. Patients with synchronous malignancies have a better outcome than the patients who have metastatic diseases in the same organs.

The aetiology remains controversial and a large number of cancer patients have to be followed for long

periods to obtain adequate data about the development of subsequent additional malignancies. Furthermore, taking into account the overall improvement in survival achieved in cancer patients in recent years and the late sequelae of cancer treatment, evidence-based long-term management and intervention strategies in order to prevent second malignancies in adult cancer survivors are required.

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None

Conflict of Interest

None declared

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