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Malignancies in Clitoris: A Review of Literature on Etiology, Diagnosis, Pathology and Treatment Strategies

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Abstract: The present study is an attempt to review literature on etiology, clinical presentation, diagnosis, pathogenesis and treatment strategies of clitoral cancer. The review emphasizes on different etiological factors represented by clinical presentations, such as infective organisms, circumcision, infibulation, clitoromegaly, priapism, vulvar cancers, ovarian cancers, mixed gonadal dysgenesis, metastasis from cancers of distant organs (adrenal glands, urinary bladder and rectal cancer), neurofibromatosis and other etiologies of tumors growing on clitoris. The diagnostic approach and pathology are interwoven on different aspects of clinical findings. The treatment strategies, including clitoridectomy, clitoroplasty, vulvectomy, lymphadenectomy, CO₂-laser treatment, laser vaporization, combined roentgenotherapy, deep x-ray irradiation and treatment for mixed gonadal dysgenesis are reviewed. This review demonstrates that there is an imperative need for more work related with case reports and review articles on malignancies of clitoris.

Key words: Malignancy, clitoris, metastasis, gynecologic cancers, distant cancers

INTRODUCTION

Clitoris, a significant part of vulva is located in the anterior region where labia minora meet. It consists of a round visible part, the glans and a long shaft, covered by tissue of labia minora, in form of a hood or prepuce. The other parts of vulva are labia majora, labia minora, openings of vagina and urethra and perineal area. Due to the presence of a high concentration of nerve endings, the function of clitoris is pleasure of sex and organisms (Qureshi *et al.*, 2007a). Any abnormality in clitoris could lead to sexual dysfunction related with arousal and/or orgasmic disorders.

Approximately 4% of all gynecologic malignancies in the United States are vulvar carcinomas with an estimated 3490 new cases diagnosed in 2007 and an estimated 880 women will die from vulvar cancer (Stroup *et al.*, 2008). Recent data show a striking increase in the incidence of Vulvar Intraepithelial Neoplasia (VIN) as a precursor lesion of the undifferentiated form of invasive vulvar carcinoma over the last 30 years in New Zealand, United States, Norway and Austria (Iversen and Tretli, 1998; Jaura, 2002; Jones *et al.*, 2005; Stroup *et al.*, 2008). In contrast, the overall incidence of invasive vulvar cancer has not changed in Austria (Iversen and Tretli, 1998), whereas in the US population, an increase of 20% between 1973 and 2000 was reported in the study of Judson *et al.*, (2006).

Although, malignancy is detected in almost all parts of vulva, the incidence differs. Bokhman *et al.* (1997) reported 73 lesions confined to vulva, 17 to labia majora and minora, 41 to the clitoris and 17 lesions to other structures. In another study on 50 patients, Popovici *et al.* (1996) found

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42 lesions to be on the labia majora, 7 on labia minora, 1 each on clitoris and Bartholin's gland. Among 360 patients diagnosed with vulvar cancer, 40 cases were found to have clitoral cancer (Masak and Hudakova, 1996).

The histologic features of a carcinoma of clitoris were found to be different from squamous cell carcinoma of vulva. It has large areas showing a transitional cell carcinoma pattern and foci of spindle and anaplastic cells, in addition to poorly differentiated non-keratinizing squamous cell carcinoma. The clitoral neoplasm was also found to differ in its cytokeratin profile from that described in invasive squamous cell carcinoma of vulva, especially with regard to the widespread staining for cytokeratin (Czernobilsky *et al.*, 1995). The localization of tumor, its size, status of lymph node and intensity and depth of invasion are some of the important prognostic factors. A large number of papers are published on vulvar cancers, including the malignancies in its different parts, however; there is a paucity of literature on cancer of clitoris. In view of (i) the significance of clitoris in normal sexual function (ii) the difference in histology of vulvar and clitoral cancers and (iii) a paucity of literature, it was found worthwhile to make an attempt to review the literature on clinical presentation, including etiology, diagnosis, pathogenesis and treatment strategies of clitoral cancers.

CLINICAL PRESENTATION, DIAGNOSIS AND PATHOLOGY

The different etiological factors responsible for clitoral cancers are (i) unprotected sex and infections from viruses and fungus, (ii) circumcision and infibulation, (iii) clitoromegaly, due to several etiologies, (iv) priapism, caused by erectogens or some pathological conditions, (v) invasion from vulvar cancers (angiokeratoma, keratoacanthoma, angiofibroma, melanoma, neurofibromas), (vi) metastasis from ovarian tumors (Sertoli-Leydic and Stromal-Leydic cell tumors, gynandroblastoma), (vii) mixed gonadal dysgenesis, including gonadoblastoma, (viii) metastasis from adrenal carcinomas and adenomas, (ix) metastasis from squamous and transitional cell carcinomas of the bladder and pelvis, respectively (x) genitourinary neurofibromatosis and (xi) vascular tumors, including hemangiopericytoma. The diagnosis and pathogenesis of the malignancies on different aspects of clinical findings are reviewed.

Infective Organisms

Unprotected sex is known to spread gynecological diseases caused by infective organisms, including fungi and viruses (Qureshi *et al.*, 2007b). These diseases, if not treated on time might become malignant and cause gynecologic cancers involving vulva and clitoris. Three cases of large vulvar lesions caused by Human Papillomavirus (HPV) are described by Nachev *et al.* (1996). One patient had condylomata covering entirely the labia majora and minora, clitoris, perineum and perianal area. The other had two big squamous papillomata of the size of 3.5 by 3.5 and 0.5 cm thick situated on both sides of commissura posterior. The third had condylomata acuminata of labia minora and majora, fossa navicularis, the perineum and the perianal area. Hampl *et al.* (2006) reported a case of an 18-year-old woman, who had fungal infection of vulva and complained of dysuria and vulvar pain. She was treated several months for infection before being diagnosed with a vulvar carcinoma located between clitoris and urethra. The tumor tested positive for HPV type 52 and the time between primary sexual contact and tumor development was less than 3 years after contamination. A case of Buschke Lowenstein tumor, or giant condyloma of vulva or clitoris was found to be diagnosed by detection of HPV 6b DNA in nucleus of the squamous epithelium showing koilocytosis (Shimano *et al.*, 1991).

The remarkable change of tumor localization to the area between urethra and clitoris might be due to the susceptibility of the non-keratinizing epithelium to injuries or tears, which are liable to facilitate HPV infection (Kondi-Pafiti *et al.*, 2008; Hampl *et al.*, 2008). Furthermore, the early onset of sexual non-penetrating contact in young adolescents, might also be sufficient for this area to become infected with HPV, resulting in an early onset pre-invasive neoplasia which can lead to invasive lesions in this localization.

Circumcision and Infibulation

The cutting of a part of clitoris is called the circumcision and infibulation is fastening of clitoris, labia minora and labia majora with a clasp and reducing the opening of vagina to less than a centimeter by stitching. These practices are thought to be of religious significance and are often practiced in African countries. The procedure is undertaken by traditional practitioners and/or nurses and is generally performed 8-90 days after birth. The complications of this practice appear early or sometimes are delayed. Inclusion of clitoral cysts, wound infection and labial adhesion are the post-operative complications. The most common complication of infibulation is inclusion of epidermal cysts within the infibulation cicatrice. The epidermal cysts of clitoris are slow growing, intra-dermal or subcutaneous tumors with a wall composed of true epidermis (Benharroch and Glezerman, 1988; Schmidt *et al.*, 1999; Ekenze *et al.*, 2007). Fernandez-Aguilar and Noël (2003) reported a painful clitoral tumor in a 27-year-old African woman suffering from vulvar pain during coitus. Subsequent diagnosis revealed it to be an amputation neuroma, perhaps a result of circumcision.

Clitoromegaly

Any abnormality of clitoris, whether it is inclusion cysts or an increased size (clitoromegaly) or a phallus (penis) like clitoris, is sometimes associated with malignancy, hence it becomes a cause of concern and is imperative to trace the origin. Acquired clitoromegaly is a symptom which occurs in severe hyper-androgenism. Other organic etiologies include clitoral cysts of various natures, invasion of gynecologic malignancies or metastasis from distant organs (Teague and Anglo, 1996). Guelinckx and Sinsel (2002) reported a case in which clitoromegaly was developed during puberty. In this case, there was neither a sign of neurofibromatosis nor hormonal disturbances. Although, temporary use of steroids was suspected, a large sebaceous cyst was detected, which was the cause of clitoromegaly. A 28-year-old woman was reported to have a prominent penis (that enlarged throughout puberty) present from when she was 12 year old. The possibilities of hermaphroditism; adrenal hyperplasia; clitoral, ovarian and adrenal neoplasms, stromal hyperthecosis, polycystic ovarian syndrome, exogenous androgen exposure, hormones and chromosomes failed to find the cause. However, upon surgical excision, a chronic inflamed epidermoid cyst was revealed (Linck and Hayes, 2002). A 1-year old girl having clitoromegaly was found to have a normal introitus, she had no inter-sex disorder. However, upon surgical intervention, the clitoral lesion was proved to be a dermoid cyst (Abudaia and Ahmed, 1999). Chase *et al.* (2006) presented a case report of a 41-year-old woman with malignant eccrine spiradenoma of the peri-clitoral region. She had an 18-month history of painful mass adjacent to the clitoris which was diagnosed to be a cystic tumor. Ten cases were reported with cysts in their clitoris, six of them were confirmed to have clitoral tumors, 2 reported localized pains, one presented with dyspareunia and another one with complaint of a sporadic discharge of white fluid from the circumcision cicatrice. These cysts were dermoid in all cases, except in two where cysts were inflamed due to rupture (Hanly and Ojeda, 1995).

Although, the common cause of clitoromegaly is hormonal, a metastatic carcinoma may be considered as a part of the differential diagnosis (Hanna *et al.*, 2004). Bohlmann *et al.* (2005) reported enlargement of clitoris as a cause of elevation of hormones or excessive production of androgen due to ovarian cancers. In such cases, gynecologic-endocrinological assessment is done to determine hyperandrogenism. In addition to the endocrinologic evaluation, the cases of clitoromegaly also requires the diagnosis of basic chromosomal evaluation. An ultrasonographic examination is included in the diagnostic work-up in case of clitoromegaly caused by cysts and/or other pathological conditions (Robin *et al.*, 2006).

Clitoral Priapism

Clitoral engorgement, pain and local irritation are the symptoms of clitoral priapism. The etiologies include erectogenic medicines used to induce sexual arousal and orgasms, pelvic tumors, blood

dyscrasia, retroperitoneal fibrosis, pelvic venous, lymphatic obstruction and a radical cystectomy of bladder carcinoma. DiGiorgi *et al.* (2004) described the case of a 48-year-old female, who had a sustained erection of clitoris with pain for a longer time. The size was measured to be 5×2.5 cm. The woman was found to have an 8×10 cm pelvic mass that was revealed to be a transitional cell carcinoma with papillary squamous component. Another case of focal priapism of clitoris was reported to be caused by a microscopic granular cell tumor. This neoplasm invades the lumen of peripheral cavernous sinuses of the crus of clitoris and is considered to be very aggressive. Caverns invaded by tumor exhibit stasis, telangiectasia and necrosis of the smooth muscle of the trabecular wall. These changes lead to collapse and compression of the cavernous spaces and cause fibrosis (Slavin *et al.*, 1986).

Vulvar Cancers

Vulvar cancer is a dreadful malignancy, which is very rare and unpleasant, but can be cured, if managed properly from the beginning. Localization of an angiokeratoma of vulva at clitoris was reported in a 24-year-old married woman. The nodule, noticed at her first pregnancy grew with occasional tenderness and bleeding during pregnancy. The growth was attributed to an increase in venous pressure or serum progesterone levels and hence this disorder was classified as a subtype of angiokeratoma of the vulva (Yamazaki *et al.*, 1992). Minderhoud-Bassie *et al.* (1992) reported the case of a 31-year-old patient with chronic complaints of vulvar itching and painful intercourse. She was under treatment with many antimycotic drugs. On examination a small tumor, on and near the clitoris was found. The tumor was clinically not differentiable from a malignant lymphoma and was proved to be a pseudolymphoma. A 33-year-old woman who presented for a keratoacanthoma of the vulva was found to have an exophytic nodule of 1 cm grown on clitoris. The nodule showed squamous proliferation (Ozkan *et al.*, 2006). Cellular angiofibroma of the vulva was reported in two middle-aged women. In each case, the lesion had the clinical appearance of a vulvar cyst, located on the lateral aspect of clitoris and the right labium majora, respectively (Dargent *et al.*, 2003).

The incidence of clitoral tumors reported in 246 patients with vulvar tumors was 5 (2%). Two of the five patients suffered from a carcinoma. The three other had benign lesions and one a hidradenoma and the other with a retention cyst and one a myxofibroma (Schiller and Donat, 1984).

Metastasis from and to Different Structures of Vulva

Malignant melanoma is uncommon in the vulva and vagina and is rare in the urinary bladder. An 80-year-old woman was reported to develop a malignant melanoma of labia majora and clitoris and subsequently developed multifocal malignant melanoma involving the vagina, urethra and urinary bladder. She underwent radical surgery but died 18 months later with liver metastases and liver failure (Kerley *et al.*, 1991). Urso and Taddei (1991) demonstrated eight cases of melanoma of the lower female urogenital tract (5 in vulva, 2 in vagina and 1 in urethra). The vulvar melanomas were polypoid and black, 3 were in major labium and 2 in clitoris. The prognosis in malignant melanoma of the clitoris was no good with metastasis to skin, lung, liver and bone was observed in many cases of malignant melanoma in genital portion (Sasaki and Ishihara, 1989).

Landthaler *et al.* (1985) reported two out of 13 patients with malignant melanoma of the vulva to have tumors on clitoris. The findings in twenty-three cases of malignant melanoma of the vulva confirmed those of earlier series that these lesions tend to occur in postmenopausal women and most commonly originate on the labia minora and clitoris (Karlen *et al.*, 1975). Low-grade Endometrial Stromal Sarcoma (ESS) within vulva was found to metastasize to clitoris and cause heavy uterine bleeding in a 46-year-old woman. A physical examination revealed it to be a lesion in clitoris (Androulaki *et al.*, 2007).

Ovarian Tumor

Sertoli-Leydig cell tumor of the ovary is reported to cause virilization in postmenopausal woman. The patient showed symptoms of masculinization, including enlargement of the clitoris. Laboratory investigations of Sertoli-Leydig cell of ovary showed elevated levels of plasma testosterone. The ovaries were macroscopically normal at operation, but pathological examination showed a small well differentiated Sertoli-Leydig cell in the left ovary (Hansen and Sorensen, 1993). Bohlmann *et al.* (2005) reported enlargement of the clitoris leading to virilization and hirsutism, as a cause of ovarian tumors with excessive androgen production. In another case (a 6 year-old-girl), clitoris enlargement and mammary development were observed to be related with elevated levels of testosterone and estradiol and an ovarian tumor. Exploratory laparotomy and definitive pathological diagnosis showed a juvenile granular cell tumor (Schulin-Zeuthen *et al.*, 2003).

An obese, diabetic, borderline hypertensive 41-year-old patient presented with complaints of masculinization had hirsutism, enlarged clitoris and increased levels of testosterone. Histology revealed stromal hyperplasia along with a 1.5 cm, testosterone-producing pure stromal-Leydig cell tumor of the right ovary (Oler *et al.*, 1999). A case of gynandroblastoma of the ovary was presented in a 17-year-old girl. The girl had primary amenorrhoea, hirsuties and slight clitoral enlargement associated with the tumor. Laboratory investigations showed high levels of circulating testosterone and estradiol, in addition to the presence of Reinke crystalloids in Leydig cell component (Anderson and Rees, 1975). Akkus *et al.* (1995) found an unusual case of persistent postpartum clitorimegaly due to ovarian hyperandrogenism. Intracorporeal injection of prostaglandin E₁ showed marked clitoral erection and increased arterial flow, as in the penis. Severe hirsutism, deepening of voice and enlargement of clitoris was observed in a 55-year-old hysterectomized woman. During laparoscopy the right ovary was found to contain a tumor 2.5 cm in diameter which had the histological features of a hilus cell tumor (Leydig cell adenoma) (Kloti *et al.*, 1980).

Mixed Gonadal Dysgenesis

Dysgenetic gonads includes abnormalities of sexual differentiation including features such as; variable exposure of androgen, variation of karyotype, absence of ovaries or testis. Incapacitation of mullerian-inhibiting substance. Iliev *et al.* (2002) reported mixed gonadal dysgenesis with testosterone-producing gonadoblastoma that caused enlargement of clitoris and conspicuous muscle development in a girl at the age of 9 years and 6 months. Biochemical analysis showed high values for testosterone and normal basal values for 17-hydroxyprogesterone and dehydroepiandrosterone sulphate. Laparotomy showed gonadoblastoma arising from testicular structures on the left and a female streak gonad on the right side with normal uterus and fallopian tubes. In a report on cytogenetic and phenotypic findings, Gantt *et al.* (1980) described mosaicism with 45,X/46,XY in 15 patients. Six patients presented with delayed sexual development without masculinization. The remaining nine patients had varying degrees of masculinization, ranging from clitoromegaly to hypospadiac male phenotypes. Cardiovascular/renal anomalies were detected in 2 of the 15 patients. Gonadoblastomas were present in two patients and did not appear to correlate with the degree of masculinization or percentage of 46, XY cells present.

Cytogenetic and molecular genetic findings in various tissues revealed a great clinical variability in Ullrich-Turner syndrome. In few cases the karyotype shows the presence of an additional Y-bearing cell line which is referred to as a borderline case of mixed gonadal dysgenesis. In this condition, Turner specific stigmata occur in about half of the cases. Bergendi *et al.* (1997) reported a case of a 10 year-old girl with short stature and only a few other signs of Turner syndrome and hypertrophic clitoris revealed 45,X/46,X,idic(Yq) mosaicism with 41% 46,X,idic(Yq) cells in a blood lymphocyte culture. The patients with normal or rearranged Y chromosome have an increased risk of developing gonadal

neoplasia. In a study on hypertrophic clitoris with separated urethral and vaginal opening, Dumic *et al.* (1993) diagnosed an infant to have 46, XY incomplete pure gonadal dysgenesis. Examination of gonads showed it to be a case of gonadal neoplasia. Barakat *et al.* (1979) described a phenotypic girl with secondary amenorrhea, enlargement of the clitoris, XY gonadal dysgenesis and bilateral gonadoblastomas. The presence of the Y chromosome was suggested to be an indication of the presence of a gonadal tumor.

Metastasis from Tumors in Distant Organs

The distant metastasis is considered to be a result of vascular or lymphatic spread and to a lesser extent by seeding of the tumor cells with urine or transurethral instrumentation.

Mediastinal Tumor

The condition of mediastinal tumor enlarges the kidneys and clitoris. A 2-year-old girl was admitted for clitoromegaly, mediastinal tumor and enlarged kidneys. A seventh cranial nerve palsy associated with an increased cell count in cerebrospinal fluid confirmed a lymphoblastic lymphoma (Ludwig *et al.*, 1987).

Adrenal Carcinoma

Carcinomatous metastases are often present in the adrenal glands, particularly the bronchial cancer. We describe here the influence of adrenal cancer on hypertrophy of clitoris. A case of virilizing adrenocortical carcinoma was reported in a 35-year-old woman. There was an incidental detection of left adrenal mass. At the time of admission, facial acne, systemic hirsutism, hypertrophied clitoris and amenorrhea for two months were observed. Laboratory investigations revealed high levels of serum testosterone and urinary 17-KS and 17-OHCS. Subsequently it was diagnosed to be adrenocortical carcinoma (Tsujimura *et al.*, 1993). A 16-month-old girl showed signs of hirsutism with low pitched voice, development of pubic hair and hypertrophy of labia minora and clitoris. Laboratory investigations showed the presence of a tumor (later diagnosed as adrenocortical adenoma) in the front upper position of left kidney. She had high levels of androstenedione, dehydroepiandrosterone sulfate and cortisol in blood, in addition to 17-KS and 17-OHCS in urine. The abdominal CT revealed a tumor in the front upper position of left kidney and adrenal scintigraphy disclosed an accumulation image in the adrenal gland on the left side (Nakagawa *et al.*, 1989). A 12-year-old girl was presented with deepening of the voice, elevated levels of serum testosterone. She was found to have a small, left-sided adrenal mass, which was subsequently identified to be adrenocortical carcinoma by computed axial tomographic scan and histopathology (Sorgo *et al.*, 1988). Ninety-five percent of 78 patients were found to have adrenocortical carcinoma with some degree of virilization, notably pubic and/or body hair, clitoris or penis enlargement and adult voice. Cushing's syndrome was present in 73% of these cases. The prognosis was age related (Sabbaga *et al.*, 1993).

The retroperitoneum X-ray, in a case of enlarged clitoris and appearance of pubic hair, demonstrated a virilizing tumor of the adrenal gland. An enlargement of the right adrenal gland and the presence of a neoplasm were discovered during surgery. Histopathology of the tumor showed a well-defined neoplasm. Histo-enzymology revealed that the tissue lacked enzyme system involving 3 beta-hydroxysteroid dehydrogenase and 17-ketosteroid reductase, activity and the tumor was identified to be as originating from the internal layers of the adrenal cortex (Neto *et al.*, 1979).

Hypertrophy of clitoris with Adrenal adenoma in one case was located due to adrenal secretion modified by dexamethasone. In another case, it was surfaced by angiography (Hartemann *et al.*, 1977). Gabrilove *et al.* (1976) reported a case which was found to have an increased titer of the urinary neutral 17-ketosteroids, which failed to decrease after treatment with dexamethasone and an adrenal tumor was demonstrable on venography. Analysis of the adrenal venous effluent revealed gradients on the side of the tumor for testosterone androstenedione, estradiol and dehydroepiandrosterone sulfate.

A case of congenital adrenal hyperplasia due to 21-hydroxylase adrenal enzyme deficiency was diagnosed in female karyotype with severe hirsutism, enlarged clitoris and absence of vagina. Computerized axial tomography showed a large cystic tumor connected to the right adrenal gland. The adrenal cortex showed diffuse hyperplasia and contained a well-defined nodule (Lewin *et al.*, 1980).

Carcinoma of the Bladder

The etiology of bladder cancer is varied, whatever is the cause of bladder cancer, the transitional cell carcinoma of the bladder is reported to metastasize to clitoris (Güven *et al.*, 2007). Yet, in another case of a squamous cell carcinoma of the bladder was shown with a clitoral metastasis in a case of an 84-year-old woman who had dysuria and a clitoral mass (Hanna *et al.*, 2004). In another case of a 75-year-old woman, Yazgan *et al.* (2004) reported clitoral metastasis of transitional cell carcinoma of renal pelvis.

Rectal Cancer

Rectal cancer and liver metastatic tumor were detected in an 84-year-old woman, who visited the hospital due to pain in the external genitals. Rectal cancer was resected, however; the pain increased after the operation and she was referred to gynaecology ward. No macroscopic abnormalities of the external genitals were found, however; a vaginal examination could not be performed due to severe pain. By local examination under anesthesia, enlargement of the clitoris was detected (Kobayashi *et al.*, 1999).

Neurofibromatosis

In neurofibromatosis, nodules of various sizes occur along small nerve branches, which generally make appearance on skin, but also in some cases involve the clitoris. Fifteen cases were reported with clitoral involvement that showed concurrent renovascular hypertension. In one of these cases, there was clitoral and renovascular involvement of neurofibromatosis, which resulted in an enlarged phallus with juvenile hypertension (Nonomura *et al.*, 1992). Neurofibromatosis of vulva was also found in a case of clitoral hypertrophy, the disorder was properly diagnosed after laparotomy followed by clitorectomy (Thomas *et al.*, 1989; Nishimura *et al.*, 1991; Griebel *et al.*, 1991).

Haraoka *et al.* (1988) showed a case of clitoral involvement of neurofibromatosis in which the clitoris resembled a phallus (penis). A young girl was shown to have circumscribed neurofibroma in the external genitalia which gave the impression of a phallus and a labio-scrotal gonad is reported. An acute anxiety state developed which, together with the genital abnormality was corrected by clitoral and labial reduction (Schepel and Tohlhurst, 1981). Literature reports documented 26 patients with neurofibromas and clitoral involvement. The clitoral lesions were found to be similar to malignant lesions of neurofibromas (Sutphen *et al.*, 1995). Solitary tumors (neurilemmoma and neuroma) were also reported to involve clitoris (Huang *et al.*, 1983; Craven and Bresnahan, 1983). An unusual case of ambiguous genitalia due to neurofibroma of the clitoris was reported to have an enlarged pseudo-phallus. The patient developed spots on buttocks, chest and abdomen (Kaneti *et al.*, 1988).

Yuksel *et al.* (2003) found clitoral involvement in a genitourinary neurofibromatosis disorder. This is reported in a 28-year-old female with clitoral enlargement. Subsequent histopathological examination revealed presence of plexiform neurofibroma.

Arteriovenous Hemangioma

A hemangioma consists of a mass of blood vessels, atypical or irregular in arrangement and size. A 4-year-old girl had a complaint of clitoral enlargement as early as when she was one year old. The prepuce was darkly purplish and the clitoral neck was enlarged without enlargement of the clitoral glans. The tumor was diagnosed to be an arteriovenous hemangioma (Ishizu *et al.*, 1991).

Vascular Tumors

A vascular tumor (Hemangiopericytoma) is believed to arise from the pericyte of Zimmermann. This was the first case of a congenital hemangiopericytoma arising from clitoris. There were approximately 10% of cases that occur in children and many of them are congenital (Brock *et al.*, 1995). A 30-year-old woman was found to have a nodule of clitoris, which was subsequently diagnosed as epithelioid hemangioendothelioma (a vascular tumor) of intermediate malignancy (Strayer *et al.*, 1992).

Nevus Lipomatosus Cutaneus

Nevus Lipomatosus Cutaneus Superficialis (NLCS) is known to affect any part of the entire body, however; there was no incidence of a case of NLCS in the clitoris, before Hattori *et al.* (2003) reported a case of congenital solitary NLCS of the clitoris. Masak and Hudakova (1998) reported Squamous cell carcinoma involvement of the clitoris in 160 patients. Forty of these cases did not confirm that the localization of clitoris was a poor prognostic factor (Masak and Hudakova, 1998). Fons *et al.* (2004) showed a squamous cell carcinoma to replace the clitoris in a 75-year-old patient.

Plexiform Schwannoma

Plexiform schwannoma is a painless tumor of clitoris. Although plexiform schwannoma is rare, it should be included in the differential diagnosis of a clitoral enlargement or mass. Chuang *et al.* (2007) found plexiform schwannoma in a 41 year old woman. The tumor was without neurofibromatosis.

Rhabdoid Tumor

Malignant rhabdoid tumors of the vulva are neoplasms which show aggressive behavior and a dismal prognosis. A case of malignant rhabdoid tumor of the clitoris occurring in an elderly patient was reported by Haidopoulos *et al.* (2002). Bond *et al.* (1994) reported a case of alveolar rhabdomyosarcoma of clitoris.

Malignant Rhabdoid tumor of clitoris has similarities with other low differentiated tumors, hence; immunohistochemical and ultrastructural assessment should always be conducted so that accurate diagnosis is achieved. Individualized extensive surgical treatment might decrease relapsing disease (Haidopoulos *et al.*, 2002).

Angiokeratoma

Angiokeratoma is a benign telangiectatic vascular tumor. A 25-year-old woman was reported to have a dark ulcerated tumor of the clitoris. On histologic examination, it was demonstrated to be an angiokeratoma. The clinical differential diagnosis of angiokeratoma and of clitoral tumors includes malignant neoplasms such as melanoma (McNeely, 1992).

Paget's Disease

Patients with clitoral Paget's disease had a higher incidence of death. Location of Paget's disease is important for prognosis; and patients with clitoral Paget's disease may require more aggressive treatment (Parker *et al.*, 2000).

Retroperitoneal Paraganglioma

Paraganglioma takes origin from the chromaffin cells of the adrenal medulla. It can also arise from chromaffin cells in other sites. A 12-year-old girl with intractable retroperitoneal paraganglioma showed enlargement of the clitoris. Her condition was diagnosed as Cushing syndrome with virilism. The adrenal gland was atrophic. The levels of plasma cortisol and serum testosterone were found to be elevated in a case of retroperitoneal paraganglioma. Immunohistochemically, immunoreactive cortisol, testosterone and dehydroepiandrosterone sulfate were detectable in the tumor cells and her condition was diagnosed as Cushing syndrome with virilism (Kitahara *et al.*, 1993).

PREVENTION AND TREATMENT STRATEGIES

Preventive Strategies

Genital Human Papillomavirus (HPV) infection is the most common sexually transmitted infection worldwide. It is well known that 90% of cases of anogenital warts are caused by HPV and HPV has been implicated in many of the gynecologic cancers, including those of vulva. Vaccines (a quadrivalent (HPV types 6,11,16 and 18) and bivalent (HPV types 16 and 18) are available and licensed in some countries. Both vaccines show a more than 90% protection against persistent HPV infection for up to 5 years after vaccination (Anorlu, 2008). The circumcision of clitoris is often related with inclusion of cysts and/or clitoromegaly, which might be the bases for clitoral malignancies. Hence, circumcision may be condemned by educating the masses who practice it. Furthermore the health professionals should educate their patients on bad genital hygienic practices, such as the use of rougher toilet paper and/or keeping the parts dirty.

Treatment Strategies

The treatment strategies reviewed are:

- Clitoridectomy to treat clitoromegaly associated with malignancy
- Clitoroplasty is performed to protect the neurovascular bundle and glans
- Vulvectomy, either alone or in combination with dissection of inguinal lymph node with subsequent photon therapy is done for vulvar cancers with malignancy of clitoris
- Gonadectomy, bilateral salpingo-gonadectomy and partial hysterectomy are performed in case of gonadal neoplasia
- Pelvic lymphadenectomy is done in case of inguinal node metastases
- CO₂ laser is used to cure cancers of vulva affecting clitoris
- Laser vaporization is done for treatment of condylomata acuminata
- Sentinel node procedure is a safe treatment option
- Battery-powered vacuum is applied in case of dysfunction of clitoris

Clitoromegaly patients with delusions of performing like male sex are given vaginal estrogens and are referred for psychological assessment and counseling. Different anticancer drugs are prescribed following surgical interventions:

Clitoridectomy

In almost all cases of clitoromegaly, due to malignancy, clitorodectomy is performed (Kobayashi *et al.*, 1999). A patient having clitoral lesion (a densely cellular mesenchymal neoplasm) that was metastasized from endometrial stromal sarcoma within vulva, was subjected to a total hysterectomy (Androulaki *et al.*, 2007). Radical clitorrectomy followed with a 2 year chemotherapy with vincristin, dactinomycin and cyclophosphamide was given to a child who had neurofibromatosis. She remained tumor free 2.5 years after diagnosis (Thomas *et al.*, 1989). Inclusion of clitoral dermoid cyst and labial fusion, were treated by complete excision of the cysts and operative separation of the labial fusion (Ekenze *et al.*, 2007). The patients who preferred local excision of clitoral Paget's disease were found to live longer than those treated with other radical treatments (Parker *et al.*, 2000). A case of clitoral hypertrophy due to neurofibromatosis of external genitalia was successfully managed by clitorrectomy (Nishimura *et al.*, 1991). In some of the cases of renovascular hypertension, there was clitoral and renovascular involvement of neurofibromatosis, which caused an enlarged phallus and hypertension. These patients were successfully treated by removal of the clitoral tumor and nephrectomy (Nonomura *et al.*, 1992).

Clitoridectomy Combined with Radiation and Chemotherapy

External beam radiation therapy is often avoided in the treatment of rhabdomyosarcoma in young children because of the long-term sequelae. Conventional brachytherapy can reduce these problems, but its use is limited in young children because of radiation exposure to parents and care-givers. Nag *et al.* (1993) reported the first use of High-Dose-rate remote (HDR) brachytherapy to treat rhabdomyosarcoma at different sites, including vagina and clitoris in young children. A case of rhabdomyosarcoma in the clitoris of a girl was treated with radical clitoridectomy, radiation and chemotherapy. Follow-up at 3 years showed no active disease (Bond *et al.*, 1994).

Clitoroplasty

Clitoroplasty with sparing of the neurovascular bundle and glans is the preferred method of management of the enlarged clitoris, in order to preserve its sensitivity and protect sexual function in women (Qureshi *et al.*, 2007a; Griebel *et al.*, 1991). Haraoka *et al.* (1988) reported that clitoral involvement by neurofibromatosis results in increasing the size which can be treated by clitoroplasty. Kaneti *et al.* (1988) found neurofibroma of clitoris that resulted from an enlarged pseudo-phallus was corrected by excision and reduction by clitoroplasty (Kaneti *et al.*, 1988).

Vulvectomy and Lymph Node Dissection

Patients of vulva cancer were treated by vulvectomy or in combination with groin dissection. The invasive squamous cell carcinoma of the clitoris should be treated, in the same way as the same tumor in other areas of the vulva, with radical surgery (Eriksson *et al.*, 1984). Karlen *et al.* (1975) reported that malignant melanoma of the vulva were treated with therapy more conservative than radical vulvectomy and regional node dissection. No patient in this series with a lesion greater than 2 cm or with clinically positive groin nodes survived 5 years.

Radical vulvectomy, bilateral inguinal lymph node dissection and subsequent photon therapy was done on a patient with a nodule of clitoris diagnosed as a vascular tumor (epithelioid hemangioendothelioma). There was no recurrence of malignancy throughout the 27 month duration of observation (Strauer *et al.*, 1992). Patients having vulvar squamous cell carcinomas were treated with radical surgery. One of these had carcinoma of the clitoris involving urethra, she was treated on additional bilateral pelvic lymphadenectomy and anterior pelvic exenteration (Fioretti *et al.*, 1992). Malignant eccrine spiradenoma of the peri-clitoral region caused a painful mass adjacent to clitoris. She underwent a partial radical vulvectomy with a bilateral sentinel lymph node sampling, after diagnosis of a cystic tumor (Chase *et al.*, 2006).

Gonadectomy

A patient (an infant) with hypertrophic clitoris and separate urethral and vaginal openings was diagnosed a typical case of gonadal neoplasia. She was subjected to gonadectomy, bilateral salpingo-gonadectomy and partial hysterectomy and the patient was raised as a girl after clitoroplasty (Dumic *et al.*, 1993). Gonadectomy was done whenever a gonadal tumor was detected to have Y chromosome to correct enlargement of clitoris, XY gonadal dysgenesis and bilateral gonadoblastomas (Barakat *et al.*, 1979).

Lymphadenectomy

Clinical series were examined for lymph gland metastases in the inguinal and pelvic regions. Many patients were found to have metastases in these lymph glands. Risk factors of 20.5 (clitoris) and 4.6% (labial) was calculated for omitting bilateral inguinal and pelvic lymphadenectomy. It was concluded that optimum therapy requires addition of pelvic lymphadenectomy to extended vulvectomy and bilateral inguinal lymphadenectomy (Krupp and Bohm, 1978). Piver and Xynos (1977) reported

surgical therapy of the carcinoma of clitoris resulted in pelvic recurrence in some patients, however; patients without initial evidence of inguinal node metastases did not develop the pelvic recurrence. It was concluded that the addition of the routine use of pelvic lymphadenectomy to radical vulvectomy and bilateral inguinal lymphadenectomy in patients with carcinoma of the clitoris is not warranted and that only those patients with histologically proven inguinal node metastases should undergo pelvic lymphadenectomy.

Surgery of Adrenocortical Carcinoma

Surgery of adrenocortical carcinoma in a girl was found to be effective treatment to normalize the elevated steroid levels, correct the size of clitoris and abnormal deepening of voice (Sorgo *et al.*, 1988). Sabbaga *et al.* (1993) reported partial and/or total resection of adrenocortical carcinoma to be dependable in children under the age of 2 years.

CO₂-Laser Treatment

Treatment with podophyllin, solcoderm and diathermy had no effect on a case of cancer in vulva affecting its different parts, including clitoris. However, a single-stage CO₂-laser treatment completely cured the cancer. In a second case of big squamous papillomata present on both sides of commissural posterior, there was no effect of podophyllin, solcoderm and surgical excision. However, she was completely cured by a single-stage CO₂-laser treatment. Extensive and/or recurrent condylomata acuminata were also treated with CO₂ laser (Grundsell *et al.*, 1984).

Laser Vaporization

A patient suffering with condylomata acuminata of the labia minora and majora, fossa navicularis, clitoris, perineum and perianal area was completely cured after two sessions of laser vaporisation (Nachev *et al.*, 1996).

Sentinel Node Procedure

Sentinel node procedure is described as a safe treatment option, when counseling a patient with unifocal early stage vulvar cancer. Taking certain guidelines into account, the sentinel lymph node procedure is known to reduce the recurrence and morbidity when compared to full inguino femoral dissection (Rasspagliesi *et al.*, 2003; Zuvela *et al.*, 2003; Van Der Zee *et al.*, 2008).

Combined Roentgenotherapy and X-Ray Irradiation

Combined treatment was employed in patients who had cancer of the external genitalia, located on small pudendal lips, clitoris and commissural labiorum. The initial step of the combined treatment included short-focus roentgenotherapy of the primary tumor and deep X-ray irradiation of regional lymph nodes (Riazantsev *et al.*, 1977).

Clitoral Therapy Device (Eros Therapy)

Several gynecologic cancers, including malignancy of clitoris and their treatment is known to cause sexual dysfunction, including sexual arousal and/or orgasmic disorders. As a noninvasive, non-pharmacologic clitoral therapy, patients are advised to use a device employing a hand-held, battery-powered vacuum to cause clitoral engorgement during foreplay and self-stimulation to alleviate sexual dysfunction (Schroder *et al.*, 2005). Sildenafil citrate (Viagra) is also reported to improve blood flow to improve the sexual arousal and erectile function of clitoris (Qureshi *et al.*, 2007a).

Psychological Assessment and Counseling

Psychiatric individuals may present with a variety of delusions including those that have sexual content or sexual implications. Krychman *et al.* (2008) described a case report of a woman with

paranoid schizophrenia, presented to a gynecologist for ovarian cancer screening. Although, gynecological examination revealed only atrophic vaginitis, the complaint evaluated revealed that the patient's ovaries were testes that produced sperm and her clitoris was a penis that was capable of erection and ejaculation. The patient was treated with local minimally absorbed vaginal estrogens and referred for psychological assessment and counseling.

CONCLUSION

The different etiological factors for clitoral malignancies are infective organisms, cysts, invasion from cancers in the vicinity and metastasis from distant organs. The diagnosis of clitoral tumors includes certain biochemical measures, histo-enzymology, surgical procedures and radiological diagnosis. The surgical procedures constitute, biopsies, laparotomy, lymph node biopsy. There are different treatment strategies, such as surgical, radiation, chemotherapy and clitoral therapy (use of vacuum to improve clitoral engorgement). Psychological assessment and counseling is done to correct the delusions. In view of the significance of clitoris as the most vital part in sexual function, there is an imperative need to focus attention on more case reports and reviews on its literature.

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