

Glassy cell carcinoma: is surgical treatment with preservation of the uterus a therapeutic option?

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Summary

Glassy cell carcinoma (GCC) is a rare and aggressive type of adenoSquamous cervical carcinoma. It affects patients at a younger age compared to the general population of patients with cervical cancer. The five-year survival is inferior to that of the other histological types. The treatment is not standardized. Radiation therapy with concomitant chemotherapy is associated with a better local control and improves oncological results. The authors report here the clinical histories of two patients with an early GCC and a desire of fertility preservation treated with radical trachelectomy with an early recurrence. They conclude that considering the rarity and aggressivity of this histological type, and the lack of evidence in the literature for its management, it would be prudent to consider GCC at an early stage as a contraindication for a radical trachelectomy.

Key words: Glassy cell carcinoma; Trachelectomy; Cervical cancer; Fertility preservation.

Introduction

Glassy cell carcinoma (GCC), is a rare histological form, recognized as a subtype of mixed adenosquamous cervical cancer, most commonly found in cervical cancer, but sometimes, in endometrial cancers or in Barrett's metaplasia. Originally described by Glucksmann and Cherry in 1956, it is a poorly differentiated variety of mixed adenosquamous carcinoma, responsible for 1% to 5.3% (mean 2%) of all cervical cancers in the series reported in the medical literature [1-3]. GCC was not recognized as an entity distinct from other cervical carcinomas until Littman *et al.* reported 13 additional cases in 1976 and proposed that it can be considered as a full-fledged clinico-pathological entity [4].

Its histological appearance is characteristic, with large, undifferentiated, non-keratinized cervical cancer cells, abundant eosinophilic cytoplasm, a clear cell membrane, and a bulky nucleus, containing a prominent nucleolus [2, 5-7]. Its incidence varies between 0.2% and 9% of all cervical cancers and can reach up to 30% of adenocarcinomas, as Guitarte *et al.* has shown in his series published in 2014 [8]. The median age was 46.9 (range 12-87) years and therefore appeared to be younger compared to patients with other cervical cancer in France (median: 51-years-old) [1, 9]. An association between GCC and pregnancy has been observed, probably due to the generally younger age of the patients.

This rare histological form of cervical cancer also appears to be associated with papillomavirus (HPV), most of which are typical strains found in cervical cancer [1, 10]. It

progresses around of the squamo-columnar junction zone or inside the endocervical canal, with an extension to the vagina and the parameters. Its progression is rapid with a higher rate of extrapelvic metastases than squamous cell carcinoma of the cervix. Local recurrences occur at the vaginal apex, parametrium, and para-aortic lymph nodes. Pulmonary, hepatic, splenic, and bone distant metastases have been observed as well. The majority of recurrences have been identified within 24 months after initial treatment [1]. GCC is historically known to poorly respond to surgery with the lowest survival rates and an unfavorable prognosis [1, 5, 11, 12]. Current guidelines for the treatment of GCC are the same as those for squamous cell carcinoma of the cervix. Due to the rarity of this disease and the lack of prospective studies, the management of GCC has not been specifically defined. Treatment protocols used in the past have not had satisfactory results [13, 14].

The authors report here the clinical histories of two patients with an early GCC and a desire of fertility preservation.

Case Report

Case 1

A 37-year-old woman, gravida 2, para1, was admitted to the hospital for post-coital vaginal bleeding occurring over three months. Gynecological examination found a less than 2 cm cervical tumor, without vaginal involvement. The cervical biopsy

identified an infiltrating squamous cell carcinoma. Lumbo-pelvic MRI confirmed the presence of a 15-mm cervical lesion, far from the endocervical os, without parametrial involvement FIGO IB1, less than 2 cm), and no suspicious lymph node nor urinary extent. SCC marker was normal. After presentation in tumor board, it was proposed to perform a pelvic lymphadenectomy, and in case of non-invasion of the pelvic ganglia, to complete the procedure by a radical interovarian hysterectomy or a trachelectomy. After discussion with the patient, it was decided to perform pelvic lymphadenectomy and radical vaginal trachelectomy. The operation and immediate outcomes were uneventful, with a discharge on the second day and normal bladder voiding. The final pathological examination found 29 metastasis-free lymph nodes. The trachelectomy specimen presented an infiltrating squamous cell carcinoma, poorly differentiated, limited to the left hemi-cervix 16×12 mm in size, with stromal invasion of 4.5 mm, and a minimum free margin of 3.2 mm laterally and 16 mm from the endocervix. In addition, complete absence of vaginal and parametrial extension was confirmed, as well as the absence of any lymphovascular space invasion.

The post-operative tumor board decided no adjuvant treatment but a close follow-up, consisting of three monthly clinical examination and cervico-vaginal smears, a first pelvic MRI at six and 12 months with no pregnancy before one year.

Unfortunately, at three months, the clinical control revealed a symptomatic patient with pelvic pain and vaginal bleeding. Clinical exam found a significant recurrent infiltration of the neo-cervix and vaginal vault, with a left lateral extension fixed at the left pelvic wall. Pathological examination of the biopsies revealed a non-keratinizing infiltrating squamous cell carcinoma. Pelvic MRI showed a 74-mm recurrence with bilateral extent to both parameters, invasion of the upper third of the vagina and extension to fascia recti. The PET CT scan confirmed an isolated uterine hypermetabolism. The SCC marker was elevated at 16 ng/ml. Tumor board decided to review of the initial pathologic slides and to perform a concurrent pelvic chemoradiation therapy to control this early recurrence.

The pathological review of the radical trachelectomy specimen finally concluded to the diagnosis of GCC with a contingent of invasive squamous cell carcinoma, whereas the recurrence consisted of an exclusive squamous cell carcinoma well differentiated.

After 45 Gy in 25 fractions in combination with weekly concomitant chemotherapy with cisplatin, MRI showed a rapid regression of the lesion with a tumor residuum of 17 mm. Vaginal brachytherapy (15 Gy) was subsequently performed. After four months, MRI showed a total remission and the SCC was 0.9 ng/ml. The last MRI performed after 13 months of the recurrence diagnosis did not show any suspicious lesion. The patient is now considered free of disease.

Case 2

A 23-year-old woman, gravida 1, para 1, with no particular history, presented at her postpartum consultation. Gynecological examination revealed a suspicious cervix. Several cervical biopsies were performed, and identified a poorly differentiated, non-keratinized, squamous cell carcinoma. Tumor cells strongly expressed CK5/6/7 and were negative for p53 and ACE. HPV 16 was positive. Lumbo-pelvic MRI showed a cervical lesion of 14 mm, without parametrial extent nor suspicious lymph nodes or other signs of distant metastasis. For this Stage IB1 less than 2 cm tumor, tumor board agreed with the proposition of pelvic lymphadenectomy guided by sentinel node detection and frozen section. If negative, a radical conservative hysterectomy or trachelectomy,

according to patient's wishes, should be performed. If nodes were positive, chemoradiation therapy was the adequate treatment. After discussion with the patient, anxious to preserve her fertility, the option of radical vaginal trachelectomy was chosen and performed as nodes were negative at frozen section. Immediate outcomes were simple, and the patient was discharged on the second postoperative day. The final histological examination showed an undifferentiated adenosquamous infiltrating carcinoma whose morphological characters were compatible with a GCC. Diameters were without LVSI and the minimal margin of excision was 3 mm, with no lymphovascular space invasion. Pelvic lymphadenectomies yielded 13 healthy nodes.

Considering this histological type, the post-operative tumor board stated on a close monitoring with three monthly examination and cervico-vaginal smears and HPV test, six monthly lumbo-pelvic MRI, no pregnancy before one year, and completely normal checkup.

Although post-operative pelvic examinations were deemed normal, the second lumbo-pelvic MRI at 12 months, showed a suspicious internal iliac lymph node. SCC marker was normal. PET CT scan confirmed the internal iliac hypermetabolism. Tumor board advocated surgery of this suspicious lesion. The laparoscopic node removal was rapidly stopped after detection of a pelvic carcinomatosis implant, confirmed by frozen section examination, in addition to suspicious lesions on the splenic capsule. A carboplatin-taxol-avastin-based chemotherapy was subsequently advocated at postoperative tumor board. After three courses of chemotherapy, the right internal iliac lymphadenopathy disappeared on the CT scan, but the perisplenic lesions were persistent. Three additional courses of chemotherapy were therefore performed. A subsequent PET scan did not show any suspicious fixation. A para-aortic lymphadenectomy was performed, and returned 16 lymph nodes all free of disease as well as perisplenic biopsies. Subsequently, 45 Gy pelvic concurrent chemoradiation was delivered. After 16-month of regular follow-up, MRI, clinical examinations and control smear did not show any sign of recurrence.

Discussion

As described above, GCC of the cervix is an aggressive subtype of cervical carcinoma, with a difficult histological diagnosis, and often underdiagnosed, despite a typical pathological appearance, in favor of other histological forms of adenocarcinoma. There seems to be a spectrum of pathological characterization for GCC, which should be considered as a poorly differentiated form of mixed adenosquamous carcinoma [2]. Thus, the authors suggest thinking of GCC in case of adenocarcinoma or adenosquamous carcinoma, to review the slide, and to declare it to rare tumor registries.

In the first reported case, the diagnosis of GCC was made after a re-reading of the slides, following rapid recurrence of the lesion. Mode of presentation is similar to other histological types of invasive cervical cancer with metrorrhagia that seems to be the predominant symptom.

The clinical behavior including the response to treatment of these carcinomas is difficult to characterize with a limited number of cases in the literature, and various treatment strategies. The distribution of stages seems to be similar to that of squamous cell carcinoma of the cervix and the ma-

majority of patients (79%) were diagnosed at Stage I or II as per the present cases; indeed both patients had Stage IB1 [1, 15].

Many studies with sufficient follow-up showed a recurrence rate of 22%. The site of recurrence was the vaginal vault and the pelvis for Stage I cancers. The recurrences were locoregional and distant for Stage II [8, 16]. In the first case, the recurrence was purely local, and distant in the second case, after three months, and one year, respectively, from the initial treatment. This observation highlights the aggressiveness and rapid progression of the tumor.

The five-year overall survival rate of cervical GCC is lower compared to all patients with cervical cancer (54.8% vs. 75%), and the five-year specific survival rate is also lower for Stages I, II, and IV, although comparable for Stage III [1, 8].

The age of the patients in the two cases reported is 37 and 23 years. The average age of patients with cervical GCC is approximately ten years younger than the average age of patients with other types of cervical cancer [1, 9]. Thus, ovarian preservation is considered by many authors during radical hysterectomy.

Conization with laparoscopic pelvic lymphadenectomy for FIGO Stage IB1 without recurrence has been reported and two cases of ovarian metastasis have been documented [17–19].

The treatment of choice of Stages I and II cervical GCC less than 2 cm, is radical hysterectomy with bilateral pelvic lymphadenectomy, while removing the lymph nodes around the common iliac, internal and external iliac vessels, and anterior to the obturator nerve [20]. In case of pelvic lymph node involvement, inframesenteric lumbar-aortic dissection is indicated [21]. It is important to identify patients with cervical cancer requiring adjuvant therapy after surgery.

High risk factors for locoregional recurrence or distant dissemination are: a large lesion; lymph node involvement, impairment of the parameters, and insufficient margins of excision [1]. The intermediate risk factors are: presence of lymphovascular space invasion, deep invasion of the cervical stroma, and tumor size greater than 3 cm [16]. Patients with cervical GCC with at least one high-risk or intermediate risk factor should receive adjuvant therapy [16].

Adjuvant chemoradiation therapy reduces the risk of recurrence and improves survival of these patients [1, 16, 21]. The principles of radiation therapy for cervical cancer should be applied in patients with GCC, in combination with cisplatin [1]. The question regarding the therapeutic strategy of patients with advanced cervical GCC is still unresolved. The large Stages IIB and III can be managed with concomitant chemoradiation or chemotherapy. Once the remission is reached, a radical hysterectomy with lymphadenectomy should be considered. In case of Stage IVB

paclitaxel-carboplatin palliative chemotherapy does not prolong survival [22]. This wide variation in the therapeutic methods does not allow drawing conclusions regarding the best management to adopt.

The cervical GCC is known to have a poor prognosis, but the development of diagnostic methods and multimodal therapies have improved the management of this disease. Stages I and II have become curable, however the prognosis of Stages III and IV remains dismal.

Radical surgery and/or radiotherapy are the only therapeutic options for patients with cervical cancer with an invasion greater than 3 mm (FIGO Stage IA2) and the majority of young women with cervical cancer are diagnosed at an early stage, and the overall cure rate is considerable. Considering that more than 25% of women with cervical cancer are under 40 years of age, and nulliparous age is increasing in developed countries, the radical surgery, and/or radiotherapy with subsequent fertility impairment leads to psychosexual dysfunction and an impaired quality of life [23–25]. This raises the question of the possibility of preserving the uterus and allowing pregnancy to occur, without increasing the risk of recurrence. In 1986, Dargent *et al.* proposed radical vaginal trachelectomy (RVT), today called Dargent operation. The technique encompasses a bilateral laparoscopic pelvic lymphadenectomy followed by a RVT. First results of this technique were published in 1994 and were immediately promising [26, 27], and rapidly followed by other experiences throughout the world [28–31]. In 1997, an international group developed abdominal radical trachelectomy (ART), then the pure laparoscopic technique, and more recently the robotic approach [32]. During the last decade, neoadjuvant chemotherapy and the preservation of fertility for more advanced cancers have been the subject of several publications, and currently studies are addressing the issue of less radical operations, especially when preserving fertility in highly selected patients [33–37].

Respect of selection criteria is the most important factor of success of this procedure. They have been clearly listed by Schneider *et al.* [28]. Firstly any cause of infertility should be tracked. Then a precise measurement of the tumor is mandatory. MRI is the most accurate imaging method. Conization is another method to obtain a precise measurement of the tumor and confirm the presence of LVSI. Tumor size is the main criteria for most of the centers. The appropriate candidates are patients with tumor less than 2 cm in greater dimension. Stage IB1 tumors larger than 2 cm are at higher risk of ectopic involvement and, statistically, the risk of recurrence is significantly higher [38, 41]. The presence of lymphovascular emboli is the most discussed risk factor [29, 30, 42]. This is not an exclusion criteria for the majority of centers, but patients should be informed of the higher risk of recurrence. Probably the density of LVSI might be a better risk factor than only presence or not. A colposcopy performed by an expert

is the standard examination before any radical trachelectomy; it allows evaluating the exocervical diameter of the tumor and its vaginal extension [29, 43, 44]. MRI is the second preoperative diagnostic examination required to determine the exact size of the tumor, infiltration of the cervical stroma, and the parameters. A healthy margin of 1 cm is required for a higher rate of pregnancy [31, 37, 45]. Preservation of the cervical stroma reduces the risk of cervical incompetence, ascending infection, and premature delivery. Frozen section of the specimen should be done to assess the extension of the tumor and the stromal margin. At least 8 to 10 mm of healthy margins must be obtained; otherwise, a cut of the endocervix must be performed or the surgery must be radicalized [40, 46-48]. On the other hand, MRI and CT scan are not able to evaluate the microscopic invasion of the lymph nodes [42, 49]. The new generation of PET seems to be useful in the preoperative evaluation of lymph nodes [50]. Transvaginal and transrectal ultrasonography are used for the evaluation of tumor size in some centers with good results [51].

From a histopathological point of view, cervical neuroendocrine carcinoma is a contraindication for a conservative surgical treatment, because the prognosis of this histological type is worse than the other types [38-40, 52]. Adenocarcinoma is not a contraindication but is considered a prognostic factor. GCC is not mentioned as a contraindication.

The evaluation of the pelvic lymph nodes has also to be performed intraoperatively and is currently executed in most centers by the sentinel lymph node technique [37, 53, 54]. This technique detects metastatic lymph nodes but is less sensitive to micro-metastases. Therefore, patients should be well-informed of the alternatives before surgery.

Both cases reported marked by the very rapid recurrence of cancer, lead us to highlight the aggressiveness of this histologic type and to consider the surgical techniques preserving the uterus and the conservation of the ovaries as contraindicated in patients with cervical GCC, and if secondarily confirmed, radical hysterectomy and systematic bilateral oophorectomy should be considered, and postoperative chemoradiation should be discussed.

Conclusion

GCC is a rare and aggressive type of adeno-squamous cervix, which can be under-diagnosed given the mixture of pathological subtypes. It affects patients at a younger age compared to the general population of patients with cervical cancer. The five-year survival is inferior to that of the other histological types. Radiation therapy with concomitant chemotherapy is associated with a better local control and improves oncological results. Considering the rarity and aggressivity of this disease and the lack of evidence in the literature for its management, it will be prudent to consider GCC at an early stage as a contraindication for a radical trachelectomy.

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