Conservative treatment of glassy cell cervical cancer: A case report

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Abstract. Glassy cell carcinoma (GCC) constitutes a rare yet histologically aggressive subtype of cervical cancer known for its rapid proliferation and high risk of recurrence and metastasis. Due to its low prevalence, the medical literature lacks large retrospective and prospective studies, and thus, no standardized management has been defined. The recommended treatment for GCC is radical hysterectomy with bilateral pelvic lymphadenectomy; however, since it mainly affects young women of reproductive age, data in the literature suggest conservative management, such as radical trachelectomy. The present report describes the cases of 2 young patients treated conservatively with pelvic lymphadenectomy and radical trachelectomy for early-stage GCC of the cervix. The first patient was a 37-year-old patient who presented a 15-mm GCC tumor [International Federation of Gynecology and Obstetrics (FIGO) stage IB1], and the second patient was a 23-year-old patient who presented a 14-mm GCC tumor (FIGO stage IB1). The first patient presented early vaginal recurrence 3 months postoperatively, which was treated with concomitant pelvic chemoradiation (45 Gy) followed by vaginal and uterine brachytherapy (15 Gy). The second patient presented internal iliac nodal recurrence 1 year after treatment, which was treated by carboplatin-paclitaxel-Avastin-based chemotherapy, followed by laparoscopic paraaortic lymph node dissection and pelvic chemoradiation (45 Gy). Both patients were tumor-free after 5 and 6 years, respectively. Due to the aggressiveness of GCC of the cervix and its high risk of recurrence, conservative treatment should be considered cautiously and should not be the standard of care.

Introduction

Cervical cancer is the fourth most common cancer in women, with an estimated yearly incidence exceeding 600,000 and a mortality rate of almost 340,000 in 2020 (1). Squamous cell carcinoma (SCC) and adenocarcinoma are the two most common histological subtypes of cervical cancer, accounting for almost 85 and 10% of all cervical cancers, respectively (2). Other histologies such as small cell, neuroendocrine, adenosquamous, and glassy cell carcinomas (GCC) represent between 3-5% of cervical cancers (3). They are commonly associated with a higher risk of recurrence and death. GCC of the cervix is a rare but aggressive subtype of cervical cancer, considered a variation of Adenosquamous Carcinoma (ASC); It accounts for less than 1-2% of all cervical cancers and is usually diagnosed at a mean age 10 years younger than other histologies (4). Possible associations were suggested between GCC and high-risk human papillomavirus infection (HPV 16, 18, 32) and recent or current pregnancies (5).

Histologically, GCC constitutes a part of the spectrum of ASC, for which pathological diagnosis is based on identifying a poorly differentiated ASC with no or rare squamous or glandular differentiation and a high mitotic rate. It can be either the predominant or focal component of the disease, with a cut-off of 85%. GCC cells are large cells with a moderate-size cytoplasm with fine granulations and a ground-glass appearance, large nuclei, prominent nucleoli, and a distinct cell wall that stains eosin and periodic acid-Schiff. This characteristic glassy appearance is related to the abundance of chromatin in GCC cells (5-7).

Owing to the rarity of GCC of the cervix, large retrospective, and prospective studies are lacking; thus, treatment strategies for GCC are based on the treatment guidelines of SCC. Radical hysterectomy preceded by bilateral pelvic lymph node dissection is the recommended treatment for early stages GCC cervical cancers (8); However, despite its aggressiveness, radical trachelectomy was also proposed as an acceptable conservative approach to treating early-stage cervical cancer in young patients wishing to preserve their fertility (9). This procedure has gained acceptance secondary to the promising oncologic and obstetrical outcomes (10,11).

Case report

We present the cases of two early-stage glassy cell cervical cancer treated conservatively.

The study conforms to the French ethical standards, and the 2008 Helsinki declaration and signed informed consent were obtained from both the patients included in this study.

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The first patient was a 37-year-old woman, gravida 2, para 1, who was admitted for post-coital vaginal bleeding for over three months. Physical examination showed a cervical tumor with no vaginal involvement. Biopsies confirmed the diagnosis of squamous cell carcinoma. Pelvic MRI showed a 15 mm cervical lesion (FIGO IB1) with no associated lymphadenopathy or signs of metastatic spread. She underwent pelvic lymphadenectomy with a negative frozen section analysis of the resected lymph nodes and a radical trachelectomy. Definite pathology analysis confirmed the 29 disease-free lymph nodes and a 16 mm slightly differentiated squamous cell carcinoma, limited to the left part of the cervix, with a minimum of 3 mm lateral safety margin. No vaginal or paracervical involvement and no lymphovascular space involvement (LVSI) were found on the surgical specimens (Figs. 1 and 2). The patient's case was presented at the multidisciplinary tumor board, and surveillance was installed. Three months postoperatively, the patient's clinical exam revealed vaginal recurrence with left lateral extension to the pelvic wall. Pelvic MRI showed a 74 mm lesion with bilateral paracervical extension, involvement of the upper third of the vagina, and extension to the fascia recti. A positron emission tomography (PET) scan revealed isolated uterine hypermetabolism. The biopsy of this lesion confirmed the recurrence of a non-keratinizing SCC (Fig. 3). Reread of the trachelectomy pathology specimens concluded a major GCC with a minor SCC component (Figs. 1 and 2), whereas the biopsy of the recurrent lesion showed only SCC. The patient's case was discussed in the tumor board, and treatment with chemoradiation was recommended. After administering a total dose of 45 Gy during concurrent pelvic chemoradiation, post-treatment MRI confirmed the regression of the recurrent lesion with the persistence of a 17 mm lesion. Therefore, the patient received an amount of 15 Gy of vaginal and uterine brachytherapy. Clinical examination and MRI performed respectively at four months and then at 5 years after treatment completion confirmed total remission.

The second patient was a 23-year-old woman, gravida one, para one, who underwent her first gynecological exam 4 years after the delivery because of disabling vaginismus. On physical exam, the cervix was suspicious, and several biopsies were performed. Pathology analysis found a slightly differentiated SCC (HPV 16 positive; P53 negative). Pelvic MRI showed a 14 mm (FIGO stage IB1) cervical lesion with no associated lymphadenopathy or other signs of metastatic spread. After the tumor board discussion, the patient underwent pelvic lymphadenectomy with a frozen section analysis followed by a radical trachelectomy. Results of definite pathology confirmed 13 disease-free lymph nodes and a 21 mm slightly-differentiated adenosquamous carcinoma with a morphologic appearance of GCC without lymphovascular invasion and minimal lateral safety margins of 3 mm (Figs. 4 and 5).

Due to the aggressiveness of this histological subtype, a close follow-up of the patient was put in place that consisted of a Pap smear and HPV testing performed at two months, followed by a pelvic MRI at four months after treatment, and contraception for at least one year. The HPV testing returned positive for HPV16, and the pelvic MRI was normal four months postoperatively. The pelvic MRI performed one year after treatment completion showed a suspicious 13 mm right internal iliac adenopathy, confirmed on the PET CT scan. The CT scan-guided biopsy of this adenopathy confirmed the recurrence of GCC, despite the normal Scc level (Figs. 6 and 7). After discussion in the tumor board meeting, a diagnostic laparoscopy before paraaortic lymphadenectomy was performed. We found suspicious pelvic lateral and peri-splenic lesions that were biopsied, contraindicating lymphadenectomy. The patient underwent six cycles of Carboplatin-Paclitaxel and Bevacizumab chemotherapy. The CT scan imaging, after three cycles of chemotherapy, showed the complete regression of the right internal iliac adenopathy but the persistence of the peri-splenic lesions. However, the PET CT scan performed after 6 cycles showed no suspicious lesions. The patient then underwent another diagnostic laparoscopy and laparoscopic para-aortic lymphadenectomy, revealing 16 disease-free lymph nodes and disease-free biopsies of the peri-splenic lesions. Concomitant pelvic chemoradiation with a total dose of 45 Gy was performed. The patient's clinical, biological, and MRI evaluation showed no recurrence after 6 years of follow-up.

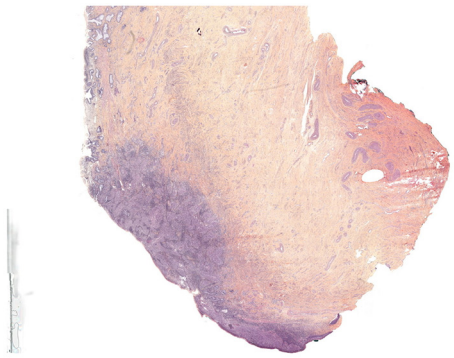

Figure 1. Initial diagnosis pathology specimen of the first patient. Magnification, x2. Neoplastic proliferation developed at the expense of the posterior part of the uterine cervix over a thickness of 4.5 mm.

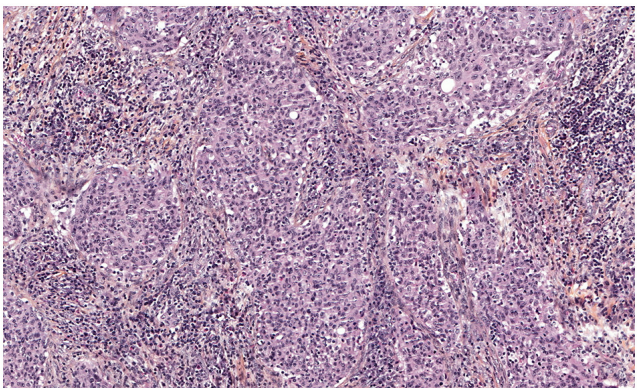

Figure 2. Initial diagnosis pathology specimen of the first patient. Magnification, x400. Poorly differentiated carcinoma arranged in the form of large, more or less anastomosing masses. The tumor cells were large, with abundant, eosinophilic, finely granular cytoplasm and a large nucleus, usually clear with a prominent nucleolus. Under the microscope, numerous figures of mitosis and marked anisokaryosis were observed. The stroma was inflammatory and rich in polynuclear eosinophilic cells.

Discussion

GCC was first described by Cherry and Glucksman (7) in 1956 as a rare subtype of cervical cancer with distinctive

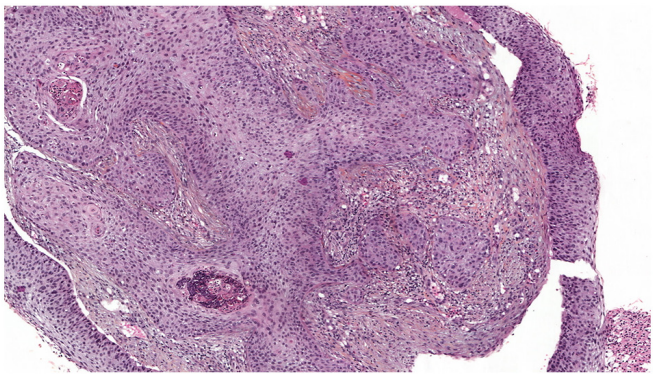

Figure 3. Recurrence pathology specimen of the first patient. Magnification, x200. Ectocervix with high-grade dysplastic epithelium infiltrated by squamous cell carcinoma. The presence of foci of squamous intraepithelial neoplasia of grade 3 was observed. Infiltrating squamous cell carcinoma was associated with it, indicating tumor masses surrounded by a fibrous-inflammatory stroma. Some of the clusters were located between large vessels. Presence of an aspect of keratinization. The tumor cells were large, with eosinophilic cytoplasm. Anisocytosis and anisokaryosis were important. Figures of mitosis were frequently observed.

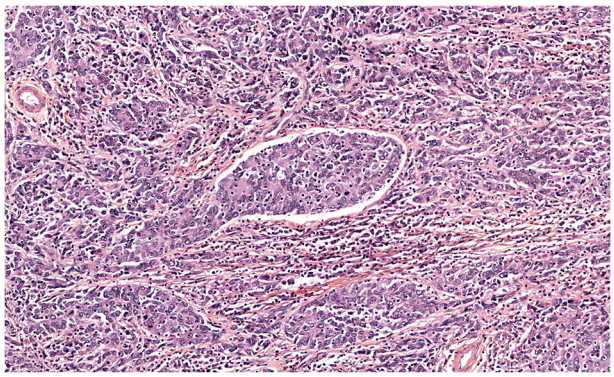

Figure 5. Initial diagnosis pathology specimen of the second patient. Magnification, x400. Poorly differentiated infiltrating carcinoma arranged in small clumps and trabeculae with poorly defined contours and focally arranged in the form of glands. The cells were small, with marked atypia; they had an atypical nucleus, often clear and glassy with a prominent nucleolus. Figures of mitosis were frequently observed. The stroma was highly inflammatory and contained numerous eosinophilic polynuclear cells.

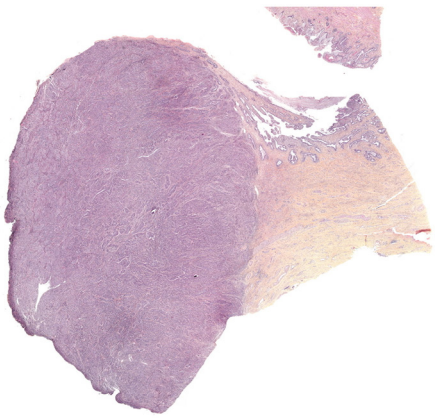

Figure 4. Initial diagnosis pathology specimen of the second patient. Magnification, x2. The presence of a tumor proliferation developed at the expense of the posterior lip of the uterine cervix over a thickness of 17 mm was observed.

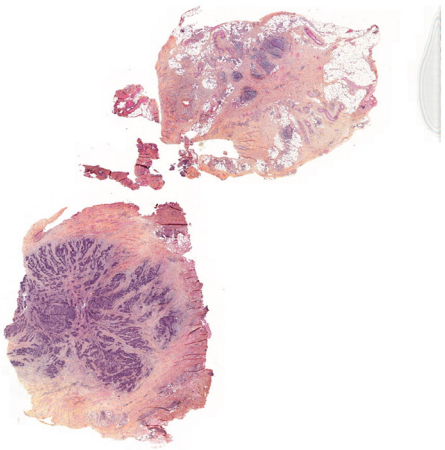

Figure 6. Recurrence pathology specimen of the second patient. Magnification, x2. Fibrous adipose tissue infiltrated by a poorly differentiated carcinoma.

characteristics, considered a variant of adenosquamous carcinoma (ASC). According to the fifth edition of the WHO classification of female genital tumors, this rare, poorly differentiated adenosquamous carcinoma grows in sheets of large cells with polygonal and abundant finely granular eosinophilic glass-type cytoplasm. Nuclei are vesicular with prominent nucleoli and numerous mitotic figures. Dense lymphoplasmacytic and eosinophilic inflammatory cells infiltrate the surrounding stroma characteristically. Intercellular bridges, dyskeratosis, and intracellular glycogen are lacking. GCC is immunoreactive for P16 (Figs. 8 and 9) (12). GCC accounts for almost 5% of all cervical cancers, 40% of which are diagnosed in reproductive-aged women (4), with a median age ranging between 28 years and 41 years, as described by Boustani *et al* (2), Hopkins and Morley (11) and Guitarte *et al* (13), respectively (2,11,13). Incidence at a younger age, with most cases presenting at early stages (stage I-II) associated with the tendency to delay motherhood nowadays, shed light on conservative and fertility-preserving strategies (2). Thus, a radical trachelectomy associated with pelvic lymphadenectomy is considered an acceptable fertility-sparing approach for treating selected patients with stage I cervical cancer (10). However, there is very little data on the conservative treatment of early-stage GCC, and this approach is still controversial (14,15).

GCC's rapid growth and poor differentiation are translated by increased aggressiveness, poorer prognosis, frequent distant metastases, and a lower response to conventional treatment modalities such as surgery, radiation, and chemotherapy (16). A meta-analysis of 292 patients showed a low 5 years survival rate of 54.8% and a median overall survival of 25 months (13). The rarity of this entity and the absence of extensive studies led initially to the adoption of the SCC guidelines in GCC treatment. However, the treatment modalities of GCC were further tailored throughout the years. In 1992, Lotocki *et al* (17) demonstrated the effectiveness of associating surgery and radiation in treating stage I GCC.

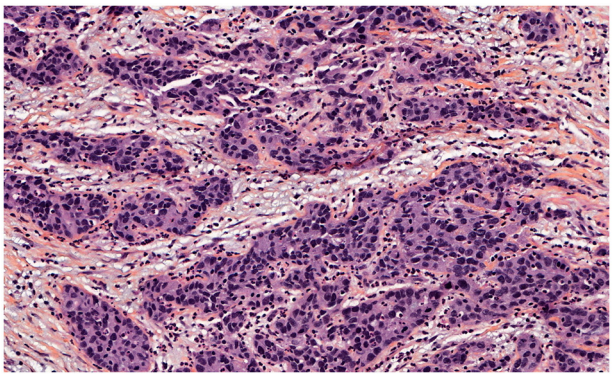

Figure 7. Recurrence pathology specimen of the second patient. Magnification, x400. The tumor was arranged in trabeculae, the tumor cells were of medium size, the nuclei were hyperchromatic and irregular, and the cytoplasm was eosinophilic.

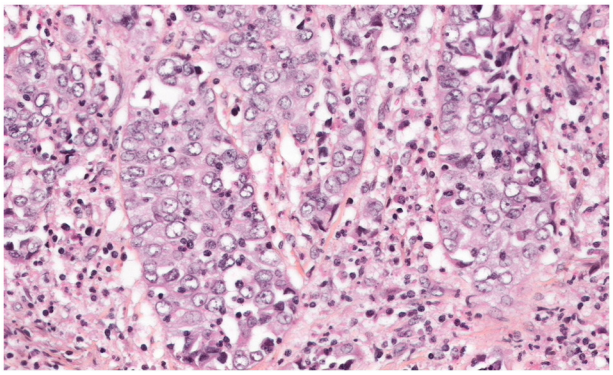

Figure 8. Initial diagnosis pathology specimen of the second patient. Typical glassy cell carcinoma tissue displaying numerous sheets of eosinophilic cells with prominent nucleoli after hematoxylin and eosin staining (histology section; original magnification, x400).

They showed a five-year survival of 45% in patients treated with surgery alone (radical hysterectomy and lymphadenectomy) compared to 87% in patients who underwent the bimodal treatment (17). Piura *et al* (8) showed in their study that multimodal treatment, including radical hysterectomy, lymphadenectomy, and concomitant chemoradiation is an efficient approach. Wang *et al* (4) showed that stage I patients treated with primary radical hysterectomy followed by pelvic radiation and monthly combined chemotherapy (paclitaxel and cisplatin) presented a DFS rate of 93% after a median follow-up of 28 months.

In their meta-analysis of 292 patients, Guitarte *et al* (13) showed that the treatment modalities for stage I were not standardized, with 44% of patients being treated with surgery alone, 32% treated with surgery followed by radiotherapy, and only 11% received trimodal treatment associating chemotherapy to the previous protocol. Recurrence rates for stage I disease were 32% for patients treated only surgically and 21% for those who received multimodal treatment. Boustani *et al* (2) evaluated the systematic preoperative brachytherapy in early stages GCC. They found that almost 70% had a complete histological response at the time of surgery, suggesting that the radiosensitivity of GCC is not drastically different from that of other cervical carcinoma (2).

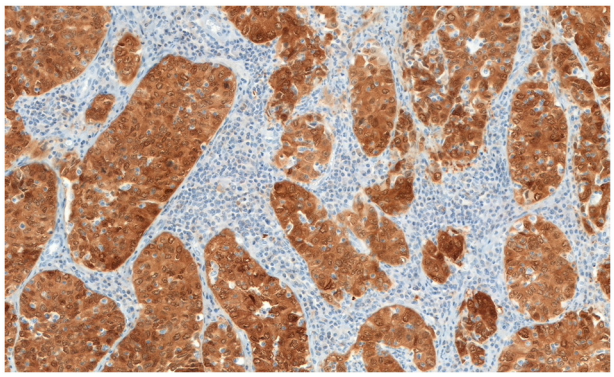

Figure 9. Initial diagnosis pathology specimen of the second patient showing the P16 immunoreactivity in glassy cell carcinoma tumor cells. Magnification, x400.

The aggressiveness and high risk of recurrence of GCC led to the exclusion of GCC patients from most cervical cancer studies. Very few reports evoke fertility preservation in GCC patients. Ferrandina *et al* (18) described a case of a 30 years-old woman diagnosed with a stage IB GCC treated with cold knife conization and pelvic lymphadenectomy. The patient refused additional treatment, and clinical follow-up showed no recurrence after 38 months. However, our experience is in line with the data in the literature. It highlights the importance of multimodal treatment even in early-stage GCC, contrary to what was described by Ferrandina *et al* (18).

In conclusion, GCC, a rare cervical cancer subtype, is frequently diagnosed in younger patients. Due to the rarity of this tumor, specific guidelines are lacking, and patients are treated following SCC guidelines. However, our experience with these two patients and the data in the literature confirm that conservative management is inadequate for early GCC patients. The multimodal approach associating radiation, surgery, and chemotherapy should remain the standard of care irrespective of the disease stage until further extensive studies are performed.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

FN, DH, HEH, EL and CP contributed to the conception and design of the study. HEH, MC, TD and AS contributed to the acquisition of data and its interpretation. HEH, DH, FN, EL, MC and TD contributed to the drafting of the manuscript. FN, EL, CP and DH contributed to revising the manuscript. All

authors agree to be accountable for all aspects of the work. HEH and FN confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study conformed to the French ethical standards, and the 2008 Helsinki Declaration and written informed consent was obtained from both patients included in the present study.

Patient consent for publication

The patients provided written informed consent for their information to be published.

Competing interests

The authors declare that they have no competing interests.

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