CASE REPORT

Endocervical gastric-type adenocarcinoma, an unrelated HPV tumour: difficulties in screening and diagnosis

Priscila Carneiro Lima,¹ Julio Teixeira,¹ Guilherme Nogueira Aires,¹
Liliana De Angelo Andrade²

¹Tocoginecology, Universidade Estadual de Campinas Faculdade de Ciencias Medicas, Campinas, Brazil
²Pathology, Universidade Estadual de Campinas Faculdade de Ciencias Medicas, Campinas, Brazil

Correspondence to
Dr Julio Teixeira,
juliotex@uol.com.br

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SUMMARY

Gastric-type adenocarcinoma of the cervix (GAS) is an uncommon and aggressive tumour unrelated to human papillomavirus (HPV) infection with distinctive histological and immunohistochemical characteristics. GAS may be associated with lobular endocervical glandular hyperplasia (LEGH), another unusual lesion. We report a case of a 59-year-old woman with screening cytology 'AGC-Neo' and cervical conisation exhibiting cervical intraepithelial neoplasia grade 1, extensive LEGH and canal sampling with abundant mucinous cells. Based on the possible association between LEGH and GAS, a total hysterectomy was performed. The histological diagnosis revealed a morphological gradient of lesions: LEGH, minimal deviation adenocarcinoma and GAS with lymphatic invasion. Immunohistochemistry revealed strong MUC6 expression and no p16 staining. After pelvic radiotherapy, the patient continues follow-up evaluation. The diagnostic difficulties of GAS and its relationship with LEGH are discussed. This rare tumour is important because it is poorly symptomatic and potentially aggressive. In addition, the methods for cancer control related to HPV do not affect this tumour.

BACKGROUND

Adenocarcinoma, typically endocervical carcinoma, represents 20%–25% of the histological types of cervical carcinoma, and the frequency of diagnosis has been increasing in recent decades.¹ Part of this increase is related to the origin within the endocervix, which is less accessible to conventional cytological screening.¹ In addition to the usual types of endocervical adenocarcinoma, approximately 10% of these lesions exhibit other less frequently observed histological subtypes, such as mucinous (gastric, intestinal or signet ring cells), clear cell, serous and mesonephric,² which may not be related to a persistent infection by a high-risk human papillomavirus (HPV).^{3,4}

The 2014 Classification of Tumours of Female Reproductive Organs by the WHO² includes gastric-type adenocarcinoma as a variant of mucinous endocervical adenocarcinomas. Minimal deviation adenocarcinoma (MDA) or adenoma malignum was recognised as a well-differentiated gastric-type adenocarcinoma. MDA histologically resembles normal endocervical glands with irregular proliferation with angular contours, desmoplastic

reaction in the adjacent stroma, and stromal deep infiltration near calibrous blood vessels without any evident atypia, which make it difficult to achieve a final diagnosis.^{3–5}

Gastric-type adenocarcinoma of the cervix is the main subtype not associated with high-risk HPV, accounting for 10%–30% of tumours.^{4,5} Its classification is based on the expression of gastric mucosa-like markers, such as mucins MUC6 and HIK1083, and a lack of DNA-HPV and p16 expression, a marker of viral oncogenic activity.^{4,6,7}

Similar to other cervical adenocarcinomas, gastric-type adenocarcinoma is difficult to diagnose and is associated with an aggressive behaviour. The current actions against cervical cancer are based on precancerous lesion detection or the prevention of high-risk HPV infection. These procedures may not affect gastric-type adenocarcinoma, a cancer that is not related to viral infection. Thus, there is a tendency for an increase in the frequency of this type of tumour. The recognition of this type of neoplasm is very important, and this case report exemplifies a gastric-type adenocarcinoma by highlighting the cytohistological evaluation, associated lesions and challenges of this diagnosis.

CASE PRESENTATION

Our study involves a 59-year-old woman with three previous births who was menopausal at age 50. She did not undergo hormonal replacement therapy and was diagnosed with diabetes mellitus type 2 and systemic arterial hypertension. Her body mass index was 27.8 kg/m². She presented with abnormal cervix cytology in a routine screening with atypical glandular cells and neoplastic favour (AGC-Neo, figure 1) in February 2014.⁸ Previous screening for cervical cancer was regular and negative.

INVESTIGATIONS

The clinical and gynaecological examination and the pelvic ultrasound did not present any abnormalities. The result of the colposcopic examination was compatible with a low-grade cervical lesion, and a biopsy revealed cervical intraepithelial neoplasia grade 1 (CIN1).

The patient reported some personal difficulties in performing the sequence of evaluations. In February 2015, she returned and was attended at the Women's Health Hospital by Professor Dr José

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Figure 1 Details of screening cytology with AGC-Neo diagnosis: dense and small clusters of glandular cells (A) exhibiting a morula-like pattern (B), papillary (C) and acinar (D) appearance involved in abundant mucus or necrosis (E). The cytoplasm is large and vacuolated; the nuclei are monotonous with finely granular chromatin and occasionally exhibit evident nucleoli (F).

Aristodemo Pinotti, CAISM, Unicamp, Campinas (SP), Brazil. This institute serves as a reference service from the Health Public System for the management of gynaecological neoplasia.

At that time, no abnormalities were noted in the clinical evaluation. A new colposcopic examination was adequate, revealing

Figure 2 Conisation of the uterine cervix with lobular endocervical glandular hyperplasia: (A) the glands are well defined as lobules and lined by mucinous epithelium with or without mild atypia; (B) the hyperplastic glands often have a pyloric phenotype, leading some authors to prefer the term 'gastric metaplasia' over lobular endocervical glandular hyperplasia; (C) endocervical margin of the cone exhibiting the same pattern of lobular endocervical glandular hyperplasia; (D) Pipelle: fragments of mucinous epithelium without atypia.

Figure 3 Hysterectomy specimen: (A) Atypical lobular endocervical glandular hyperplasia with glandular complexity and intraglandular bridging (arrow); (B) area of minimal deviation adenocarcinoma: glands without atypia with angular outlines invading the stroma; (C) gastric-type adenocarcinoma with cellular atypia; (D) MUC6 immunohistochemical positive expression in the cytoplasm of endocervical gastric-type adenocarcinoma. Carcinomatous emboli were also observed and are marked (arrow).

transformation zone type 2 (a fully visible squamous-columnar junction partially located in the endocervix) and the presence of a thin acetowhite epithelium (2 hours) and fine mosaic (6 hours) located inside the transformation zone.⁹ The corresponding biopsies also indicated CIN1 in both areas.

A cytological review was performed with confirmation of the result of AGC-Neo. A pelvic ultrasound revealed retroverted uteri (36.8 cm³), a subserous uterine myoma in the anterior wall (33×26 mm), a 4 mm endometrial line and an echogenic image suggestive of a polyp in the posterior wall (4.1×2 mm). Due to the persistence of the changes, a loop electrical excision procedure (excision of transformation zone type 2) of the uterine cervix was performed in July 2015. A single cone specimen was obtained containing the transformation zone⁹ that measured 27×25 mm at the base and 15 mm in length, and biopsies of the canal and endometrial cavity using a Pipelle device (Pipelle de Cornier for endometrial biopsy; Laboratoire CCD, Paris, France) were obtained.

The materials for histopathologic evaluation were processed according to the routine methods of the laboratory of Anatomic Pathology, which performed a histological study of the entire specimen and characterisation of the margins of cone resection previously marked with Nankin ink. The histological analysis revealed focal CIN1 and extensive lobular endocervical glandular hyperplasia (LEGH, figure 2A,B) that compromised the endocervical resection margin of the cone (figure 2C). In Pipelle's material, no endometrial mucosa was present, but a large amount of mucinous epithelial fragments without atypia similar to LEGH was observed (figure 2D).

After these results, the patient underwent a hysteroscopy in September 2015, which revealed no abnormalities. Thus, due to the extensive LEGH compromising the cone margin, an extra fascial hysterectomy with a bilateral salpingo-oophorectomy was performed in December 2015. Gross specimen evaluation revealed a uterus measuring 65×60×30 mm, and the cervix (postconisation) globally increased measuring 20×10 mm at the base and 25 mm in length. A histological gradient of lesions was observed in the cervix: typical and atypical LEGH with complex proliferation

(figure 3A) next to areas of well-differentiated adenocarcinoma or MDA (figure 3B) and a gastric-type endocervical adenocarcinoma that was moderately differentiated (figure 3C) measuring 11 mm laterality and 6 mm in invasive depth. Angiolymphatic space invasion by tumour cells was also detected.

DIFFERENTIAL DIAGNOSIS

The immunohistochemical panel revealed strong MUC6 positivity in neoplastic cells (figure 3D), but the lesion was p16 negative.

TREATMENT

Abdominal and pelvic tomography was performed in March 2016, with the absence of the uterus and ovaries (postoperative status) and without lymph node enlargement or other changes, leading to a diagnosis of Stage IB1 cervical cancer.¹⁰ Adjuvant pelvic radiotherapy (teletherapy and high-dose rate brachytherapy) was administered and subsequently completed in June 2016.

OUTCOME AND FOLLOW-UP

The patient has been undergoing follow-up without any clinical or imaging evidence of disease as of December 2016.

DISCUSSION

This case represents an unexpected diagnosis of cervical cancer in the hysterectomy specimen in spite of numerous propaedeutic procedures. With the exception of the 'AGC-Neo' result in the screening cytology, the cone specimen, endocervical biopsy and hysteroscopy were all negative for malignant lesions. The difficulty in detecting cervical adenocarcinoma and the low reproducibility of glandular atypia in cytological diagnoses are well known.^{5 8} LEGH is an uncommon lesion (figure 3A) and was present both in the endocervical margin of the cone and in Pipelle material from the endocervical canal. The association between LEGH and gastric-type endocervical adenocarcinoma is described in the literature^{7 11 12} and is an important factor for the indication of hysterectomy in the present case, thus allowing the definitive diagnosis.

Approximately 90% of cervical adenocarcinomas are associated with a persistent high-risk HPV infection, mainly HPV-16, HPV-18 and HPV-45.¹³ On the other hand, more recently, some publications have described histological subtypes of adenocarcinoma that are not associated with HPV, such as clear cell, mesonephric and gastric-type.^{2 6} Although 28% of clear cell adenocarcinomas are related to high-risk HPV, 100% of gastric-type endocervical adenocarcinomas are not related to HPV.³⁻⁵ The lack of p16 expression in the present case supports the different pathogenesis, which is unrelated to HPV, and a strong reaction to MUC6 reveals the pyloric-gastric profile of these mucinous carcinomatous cells (figure 3D).

The terms LEGH and 'pyloric gland metaplasia' describe the same benign pseudoneoplastic endocervical process arranged in a lobular pattern resembling MDA.^{5 11 12} Histologically, LEGH is located more superficially in the endocervical canal with delimited gland distribution, generating a lobular aspect. When the glandular pattern presents greater complexity, papilliferous arrangement, focal cellular atypia or mitotic figures, the lesion is referred to as atypical LEGH.^{4 6 12}

The immunohistochemical expression of pyloric mucins HIK1083 and MUC6 in both LEGH and gastric-type adenocarcinoma potentially contributes to the common pathogenesis, and some authors consider LEGH as a precursor lesion of MDA or gastric-type adenocarcinoma.^{6 11 14} Recent findings have identified gene mutations that suggest MDA is an evolutionary lesion due to LEGH progression.¹⁵ Gastric-type adenocarcinomas are

present in the upper endocervix as a bulky cervix, are typically p16 negative, demonstrate gastric differentiation in immunohistochemical reactions, and may be associated with LEGH, the putative precursor.^{5 11}

The few gastric-type adenocarcinomas reported typically exhibited an aggressive behaviour and unfavourable prognosis. Patients with gastric-type adenocarcinoma can appear with a clinically normal or globally enlarged cervix. In some cases, aqueous vaginal discharge is reported.¹² The cancer tends to present at an advanced stage and with a poorer survival even when matched by stage. Metastatic sites include omentum, liver, brain and bone.¹⁴ It is not known whether the poor prognoses of these lesions are attributed to the aggressive characteristics of the tumour, resistance to adjuvant therapy, diagnostic difficulties with delayed diagnosis or suboptimal surgery, or a combination of these factors.¹⁴

In our case, a gradient of histological lesions was observed: typical LEGH and LEGH with mild atypia, areas of MDA and moderately differentiated gastric-type adenocarcinoma. LEGH detected initially in the cone specimen was considered as a guide for the investigation and suggested the need for a hysterectomy. However, LEGH is an uncommon cervical lesion that is often incidentally diagnosed in cone or hysterectomy specimens and remains poorly recognised by pathologists.⁴ With a LEGH diagnosis, it is important to note the possibility of evolution to or concomitance of a gastric-type adenocarcinoma.^{4 6 12} However, this association may not always be noted, and the gastric-type adenocarcinoma may be a 'de novo' lesion or derived from gastric-type adenocarcinoma in situ.⁷

In the present case, the persistent investigation allowed the diagnosis of an invasive adenocarcinoma that was small in size (11×6 mm) but already exhibiting vascular invasion, confirming the aggressiveness of the gastric-type adenocarcinoma.

Although the cervical gastric-type adenocarcinoma is currently rare, it is possible that this type of tumour may become relatively more common in the future with the subsequent reduction in HPV-related carcinomas due to screening and vaccination and should be better studied.

In conclusion, due to the diagnostic difficulties and aggressive behaviour of gastric-type endocervical adenocarcinoma, pathologists should be aware of this rare histological type and recognise its possible precursor lesion, LEGH. Faced with a LEGH diagnosis, clinicians should also be aware of the need for persistent follow-up and investigation aiming for the early detection of this rare adenocarcinoma to achieve a relevant impact on survival.

Learning points

- ▶ Endocervical gastric-type adenocarcinoma is an aggressive disease even if diagnosed at an early stage. This adenocarcinoma is typically asymptomatic and not related to human papillomavirus (HPV) infection.
- ▶ Lobular endocervical glandular hyperplasia, another uncommon lesion, is frequently associated with the diagnosis of a gastric-type adenocarcinoma of the cervix.
- ▶ The final diagnosis is difficult and may be obtained after a detailed histologic evaluation by gynaecologic pathologists and MUC6 (+) and p16 (–) immunohistochemical reactions.
- ▶ Cervical cancer control measures (screening by HPV tests and prophylactic vaccination) will not impact adenocarcinomas unrelated to this virus, including the most important type of adenocarcinoma, gastric-type adenocarcinoma, as presented in this report.

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