Squamous cell carcinoma of uterine cervix with osteoclast-like giant cells: A case report

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Abstract. Squamous cell carcinoma (SCC) is a common tumor of the uterine cervix, usually related to human papillomavirus (HPV). While osteoclast-like giant cells (OGCs) have been reported to be associated with tumors at various locations, to the best of our knowledge, only six cases have been reported in the cervix to date. The present study describes the case of a 38-year-old woman with a medical history of ectopic pregnancy and vaginal childbirth, who presented with coitorrhagia. On physical examination, a mass of ~4 cm was found in the uterine cervix. A biopsy of this lesion revealed infiltrating SCC, leading to a radical hysterectomy 2 months later. The surgical specimen displayed an exophytic lesion with a maximum diameter of 3.5 cm confined to the uterine cervix, histologically consistent with an infiltrating non-keratinizing SCC. There was a prominent intra- and peritumoral chronic inflammatory reaction, and a high number of OGCs. Immunohistochemically, tumoral cells were positive for cytokeratin βE12, epithelial membrane antigen, p40, p63 and p16, and negative for CD68, vimentin and CD163. OGCs exhibited an inverted expression pattern, with positivity only for histiocytic markers. PCR for HPV detection revealed a HPV 34 genotype (probable high oncogenic risk). This profile suggests the non-neoplastic nature of OGCs, i.e. they should be considered as part of the immune response to the tumor. To the best of our knowledge, this case is the seventh instance of SCC with OGCs in the uterine cervix. Similar findings in other organs, such as the breast, pancreas or stomach, have been associated with a favorable prognosis. While two of the three reported cases with poor outcomes in the uterine cervix had an associated sarcomatoid component, the limited number of cases described to date in this location does not yet allow for an accurate prediction of behavior.

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Abbreviations: SCC, squamous cell carcinoma; HPV, human papillomavirus; OGCs, osteoclast-like giant cells; CK, cytokeratin; EMA, epithelial membrane antigen

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Introduction

Cervical cancer is the fourth most frequent cancer among women globally. Squamous cell carcinoma (SCC) constitutes the majority of these malignant tumors representing 80-90% of all cancers in this location. Typically affecting women in their sixth decade of life, patients with small tumors often do not show symptoms, while larger tumors can manifest with abnormal vaginal bleeding, discharge, and pain.

Most cervical SCCs are human papillomavirus (HPV) related. Notably, HPV-related SCCs are usually less aggressive than their HPV-independent counterparts and they arise from high-grade squamous intraepithelial lesions (HSIL). Among the multitude of HPV genotypes, types 16 and 18 stand out as the predominant contributors, implicated in the majority of cervical SCC occurrences (1).

The epidemiological landscape of cervical cancer has witnessed significant transformations, especially in high-income countries, where a decrease in both incidence and mortality rates has been observed. This decline can be largely attributed to the implementation of screening programs and the widespread HPV vaccination initiatives. These measures have played a crucial role in reducing the impact of cervical cancer and preventing its harmful effects (1).

Histologically, SCCs display infiltrative nests and cords within a desmoplastic or inflammatory stroma. Nuclear pleomorphism and increased mitotic activity characterize these lesions. Various subtypes, including non-keratinizing, keratinizing, basaloid, warty, and papillary SCCs, exhibit distinct features and a subtype of squamous cell carcinoma with giant osteoclast-like cells has not been defined.

Immunohistochemistry plays a vital role in diagnosing HPV-associated SCCs, with p16 immunohistochemical testing recommended in conjunction with molecular HPV typing.

Osteoclast-like giant cells (OGCs), characterized by their multinucleated appearance and resemblance to osteoclasts, have been described in association with some malignant tumors at various anatomical locations, e.g. the skin, breast

and pancreas (2,3). Despite their rarity, these unique cells have captured attention due to their potential diagnostic significance and implications for tumor biology. To the best of our knowledge, only six cases of SCCs with OGCs in the uterine cervix have been reported to date (4-8). This limited incidence underscores the importance of meticulous observation and thorough histopathological examination to identify and characterize such atypical tumor features within the cervix.

Case report

We present the case of a 38-year-old woman with a medical background of ovarian ectopic pregnancy in 2013 and one vaginal childbirth in 2020, who underwent periodic cervico-vaginal cytological screening, the last of which was performed in November 2017 with no remarkable findings. In September 2021, she consulted with the main complaint of coitorrhagia at Germans Trias i Pujol University Hospital (Barcelona, Spain). The abdomen was depressible and no signs of peritonism or palpable masses were detected. On vaginal examination, a mass of approximately 4 cm was found in the posterior lip of the uterine cervix, from which a biopsy was taken.

Magnetic resonance showed intimal contact of the mass with the vaginal posterior wall and suspicion of parametrial affection. Furthermore, an enlarged lymph node was found in the left external iliac region, with no evidence of retroperitoneal lymphadenopathies (Fig. 1).

The histological study on biopsy revealed a solid proliferation composed of epithelial cells with abundant eosinophilic cytoplasms and without evident intercellular bridges or keratin pearls and enlarged and hyperchromatic nuclei, thus a diagnosis of non-keratinizing SCC was made. Immunohistochemistry showed a block positive expression of p16.

Two months later, radical hysterectomy and iliac-obturator lymphadenectomy with ovarian preservation were performed. The specimen exhibited a 3.5x3x2.1 cm exophytic lesion growing at the posterior lip of the uterine cervix, with no other structures affected, and a free closest margin of 2 mm at left parametrium. No metastatic lymph nodes were found; thus, the patient was a candidate for follow-up.

The histological morphology of the mass was similar to the one previously described in the biopsy sample. High-grade squamous intraepithelial lesion was found in the tumor boundaries, and an intense intra and peritumoral inflammatory reaction was noted, mostly lymphocytic, with a striking number of multinucleated OGC-like cells. These cells were heterogeneously distributed throughout the tumor with no evidence of clustering. The previous biopsy sample was then reviewed, and some OGCs were retrospectively observed (Fig. 2).

Immunohistochemistry was performed on whole tissue sections using CC1 (Roche, Ventana Medical Systems) for antigen retrieval and HRP Multimer as secondary antibody (Roche, cat. no. 253-4290, pre-diluted 55 μg/ml). Counterstaining consists in two steps; hematoxylin (16 min) and bluing reagent (4 min) for all the antibodies. The used antibodies for this study were: CKβE12 [34 βE12 (Roche) 95˚C, 32 min (cat. no. 790-4373) pre-diluted 1.4 μg/ml], EMA [E29 (Roche) 95˚C, 32 min (cat. no. 790-4463) pre-diluted 0,5 μg/ml], p40 [BC28 (Roche) 36˚C, 48 min (cat. no. 790-4950) pre-diluted 0.4 μg/ml], p63 [4A4 (Roche) 95˚C, 52 min (cat. no. 790-4509) pre-diluted 0.14 μg/ml] p16 [E6H4 Histo (Roche) 95˚C, 32 min (cat. no. 805-4713) pre-diluted 1.0 μg/ml] CD68 [kp-1 (Roche) 95˚C, 32 min (cat. no. 790-2931) pre-diluted 0.4 μg/ml], CD163 [MRG-26 (Roche) 37˚C, 32 min (cat. no. 760-4437) pre-diluted 0.19 μg/ml], p53 [DO-7 (Roche) 95˚C, 56 min (cat. no. 800-2912) pre-diluted 0.5 μg/ml] and Vimentin [V9 (Roche) 95˚C, 32 min (cat. no. 790-2917) pre-diluted 2.5 μg/ml]. Positive staining was defined according to ASCO/CAP guidelines.

Epithelial cells showed CKβE12, EMA, p40, p63 and p16 block expression, and no reactivity for vimentin, CD68 and CD163. p16 positivity led to HPV analysis, so DNA from the sample was PCR amplified with the VisionArray® HPV PreCise Master Mix (ES-0007-50, Zytovision) and genotype obtained after hybridization with the VisionArray® HPV Chip 1.0 (VA-0001-10, Zytovision), which allows the detection of forty-one different types, obtaining a positive result for viral HPV 34 (classified as probable high oncogenic risk) (Fig. 3). A negative result was obtained for HPV 16, 18 and other high risk types.

OGCs were reactive to vimentin, CD68 and CD163 and negative for CKβE12, EMA, p40, p63 and p16, elucidating an inverted expression profile compared to the epithelial cells (Fig. 2). Staining with p53 showed a wild-type pattern expression in both cell populations. Therefore, the final diagnosis was a non-keratinizing poorly differentiated (G3) SCC with HPV-associated OGCs, stage IB (FIGO 2008).

Discussion

While there are various tumors whose neoplastic cells can show OGC morphology, neoplasms with non-neoplastic OGCs have been also described, some of which have been accepted as new entities.

The case we report could be one of these tumors with immune response associated giant cells, the significance of which is still not well understood. There are some data to support this hypothesis. Firstly, the immunohistochemical expression of macrophagic-histiocytic markers in the OGCs and the associated prominent lymphocytic infiltrate suggest a reactive origin. Moreover, some cases described in the skin (9) and the pancreas (3) have been related to a p53 mutational pathway with an immunohistochemical aberrant expression in tumor cells as a surrogate marker and a wild-type phenotype in associated OGCs. However, this is not the scenario in our case, since the main mutational pathway is probably associated with HPV, and p53 shows a wild-type expression in both the epithelial cells and OGCs. Finally, the non-neoplastic origin of these giant cells has been confirmed by molecular analysis in OGCs associated with ductal pancreatic adenocarcinoma, based on their diploid nature and the absence of KRAS mutations (10,11). The consistency of these results and the number of cases reported to date in the pancreas has led to the definition of a new entity in the latest edition of the WHO classification of tumors (12) i.e. 'undifferentiated carcinoma with osteoclast-like giant cells'.

Although the nature of the OGCs remains uncertain some researchers propose a syncytial fusion of macrophages,

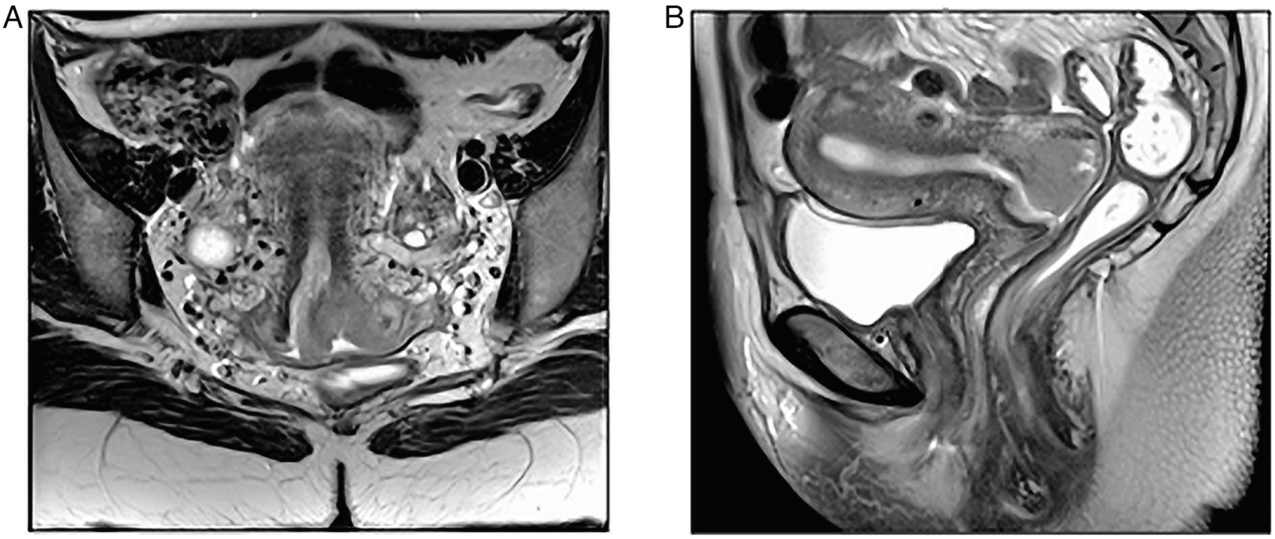


Figure 1. Magnetic resonance imaging. (A) Coronal section: Mass occupying uterine cervix. (B) Sagittal section: Mass in intimal contact with the vaginal posterior wall.

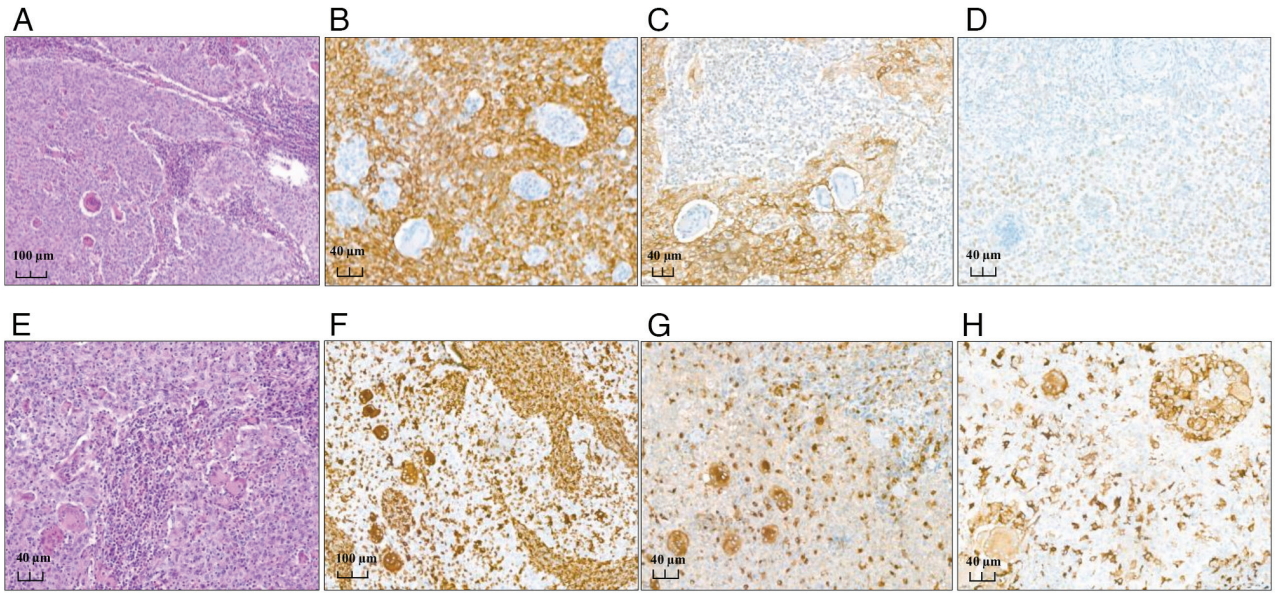


Figure 2. Histological features of the tumor and immunohistochemistry. (A) SCC with OGCs (magnification, x20). (B) Diffuse staining of epithelial tumoral cells with CKβE12, (C) EMA and (D) p40. (E) SCC with OGCs (magnification, x40) (F) Staining of OGCs with vimentin, (G) CD68 and (H) CD163. SCC, squamous cell carcinoma; CK, cytokeratin; EMA, epithelial membrane antigen.

mirroring the process observed in osteoclastogenesis. The osteoclast maturation is regulated by the expression of cytokines, which are also expressed in tumor-associated macrophages and immune cells, so it is hypothesized that OGCs share molecular features with macrophages present within the tumor (13-15). In fact, in the context of breast and pancreas cancer, it has been noted that this type of tumors present a highly vascularized microenvironment alongside inflammatory cells (lymphocytes, histiocytes) (15,16). In other locations such as skin or uterine cervix these characteristics are not so well defined.

Besides this, the significance of this type of immunological response is still unknown. The biological behavior of these tumors is not well studied; in terms of recurrence and metastasis this tumors do not appear to have distinctive histological characteristics. In breast cancer, prognosis seems to be related to the intrinsic characteristics of the carcinoma and is not associated with the presence of OGCs (17). Similar cases have been described in lung (18) and skin squamous carcinomas (9), where the prognosis and clinical behavior is uncertain. In the urinary bladder, OGC associated carcinomas seem to have an aggressive course, but it is worth noting that most of the cases have been diagnosed as undifferentiated carcinomas (19). In the pancreas, however, most cases seem to have a better prognosis than the usual undifferentiated carcinomas (20).

As is well known, the vast majority of cervical SCCs are associated with high-risk HPV genotypes, of which 70% are

Table I. Review of the cases of uterine SCC associated with OGCs.

Case	First author, year	Age, years	Tumor diameter, cm	Growth pattern	Stage	HPV PCR	Histological type	Treatment	Status	Follow-up period	IHC staining of OGCs	(Refs.)
1	Pang, 1998	65	6	Exophytic	Ib2	Not reported	Sarcomatoid	SP, RT and CT	DOD	7 weeks	CD68	(4)
2	Pang, 1998	61	5	Exophytic	Ib2	Not reported	Sarcomatoid	SP, RT and CT	DOD	14 months	CD68	(4)
3	Singh *et al*, 2012	60	4.5	Infiltrating	Ib2	Negative	Non-keratinizing	RT and CT	ACR	6 months	CD68	(5)
4	Yu *et al*, 2014	84	5	Exophytic	Ib2	Not reported	Non-keratinizing	RT	DOD	8 months	CD68, vimentin	(6)
5	Alemán-Meza*et al*, 2014	49	2.7	Exophytic	Ib1	Not reported	Non-keratinizing	SP	ACR	7 months	CD68, vimentin	(7)
6	Dejima *et al*, 2020	49	2.5	Not reported	Ib1	16	Non-keratinizing	SP, RT and CT	ACR	22 months	CD68, CD204	(8)
7	Present case, 2023	38	3.5	Exophytic	Ib2	34	Non-keratinizing	SP	ACR	24 months	CD68, vimentin	-

Tumor stage was designated in accordance with the International Federation of Gynecology and Obstetrics staging (2008) (21). IHC, immunohistochemistry; SCC, squamous cell carcinoma; OGCs, osteoclast-like giant cells; RT, radiotherapy; CT, chemotherapy; SP, surgical procedure; DOD, dead of disease; ACR, alive with complete regression.

Figure 3. HPV evaluation with Vision Array Technology. Amplified DNA is hybridized in the HPV Chip 1.0 (Zytovision) which allows the detection of high risk genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59, other probably high risk and low risk types. The HPV Chip is scanned and processed by the VisionArray® Analyzer Software that in the present case highlights the 34 type detected in an orange spot. Controls are marked as blue spots. HPV, human papillomavirus.

caused by types 16 and 18. In the cases of SCC with OGCs reported to date, PCR for HPV detection has been performed in only three of them, and just two were HPV related, with association to types 16 (case 6) (8) and 34 (present case) (Table I). HPV type 34, in contrast to type 16, is reported in the literature as a probable high oncogenic risk genotype and is less frequently found. Morphological differences have not yet been described between the most prevalent types of HPV-associated SCC; thus, it is difficult to find an association between the OGC variant and the subtypes of HPV. Therefore, it would be interesting to genotype all the cases to establish a possible relationship with morphology.

This case, the seventh with these characteristics in the uterine cervix, is the first reported in Europe and notably involves the youngest patient in the total series (Table I). Due to the small number of cases of SCC with OGCs in this location, clinical behavior and prognosis are still not clear.

Nevertheless, it is important to note that two out of the three cases reported with a poor outcome had additionally a sarcomatoid component (4), which in itself could have explained the ominous evolution. Although our patient achieved 24 months disease-free survival with an IB2 stage at diagnosis, the remaining reported cases had shorter follow-up periods, hence at present there are not enough survival data to draw robust conclusions.

Some of these cases may have gone unnoticed, possibly due to the associated lymphocytic inflammatory component so OGCs can easily be overlooked among the eosinophilic background of epithelial cells. This is further compounded by a lack of knowledge about this variant. It is therefore advisable to report each case presenting these histological features to contribute to increasing the available dataset, which would

help to clarify the relationship between etiology, morphology and prognosis. Following this approach, as happened with other locations, a new subtype of carcinoma could potentially be defined in the not-too-distant future if a correlation with prognosis is demonstrated.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

MJ and LV were involved in patient diagnosis, and in the study conception and design. AC, CS, CPF and JGG collected the data and performed the critical analysis. AC, JGG and CS generated the figures and table. The draft of the manuscript was made by AC, CPF, CS and MJ. AC and MJ confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent has been obtained from the patient.

Competing interests

The authors declare that they have no competing interests.

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