

Small cell carcinoma of the vulva: case report

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Abstract

Neuroendocrine tumours are rare in the gynaecologic tract, comprising approximately 2% of all gynaecological tumours. They have an aggressive behaviour and are a diagnostic and clinical challenge, due to their rarity and the lack of standardized therapeutic approaches. There are a few case reports. It is defined as a high-grade carcinoma exhibiting neuroendocrine differentiation. The authors describe the case of a 70-year-old woman, with vulvar neuroendocrine small cell carcinoma after superficial vulvectomy. The patient was submitted to a surgery with wide local excision and adjuvant radiation therapy. A review of the literature on this topic is also presented.

Case Report

A seventy year-old woman presenting gradual evolution pruritus gets worse recently. At clinical examination, both labia were observed as white plates, dispersed, irregular borders and sanded surface, suggestive of high-grade intraepithelial vulvar neoplasia. She was undergone to a vulvar polyp that revealed a high-grade vulvar intraepithelial neoplasia, so it was decided superficial vulvectomy. The pathological examination revealed vulvar intraepithelial squamous neoplasia of high-grade, without evidence of invasion of the underlying stroma with signs of HPV infection, diffusely involving both lips, which developed in condyloma plan context, coexisting neuroendocrine carcinoma of high-grade small cell with lymphatic tumour embolization. Discrete parakeratosis and dense inflammatory infiltrate, predominantly lymphocytic, was observed in both lips. The neuroendocrine lesion is a mass of intermediate size cells with high nucleus / cytoplasm ratio, hyperchromatic nucleus, some pleomorphism, with necrosis and figures of mitoses.

The lesion is surrounded by inflammatory infiltrate mononucleate (Figure 1A). The immunohistochemistry was positive for AE1/AE3, CK7, EMA, CAM5.2 and BerEp4, and negative for CK5, P63, CK20 and TTF1. The CD56 expression was accessed (Figure 1B). It is also observed immunostaining for neuroendocrine markers synaptophysin and chromogranin A (Figure 1C and D), with a proliferative activity assessed by Ki67 about 100%.

The patient was undergone to a complementary radical vulvectomy and bilateral lymphadenectomy. Pathological examination of the surgical specimen revealed squamous intraepithelial lesion of low grade, with no evidence of residual carcinoma or neuroendocrine tumour lymphatic embolization, and solid metastasis in 1 of the 6 right inguinal nodes of neuroendocrine carcinoma small cell without contralateral inguinal lymph node metastasis (Figure 2). It was given adjuvant radiation therapy after wide local excision.

Discussion

Neuroendocrine tumours have an aggressive behaviour and are a diagnostic and clinical challenge, due to their rarity and the lack of standardized therapeutic approaches.¹ They are defined as a high-grade carcinoma exhibiting neuroendocrine differentiation.^{2,3}

They are rarely found in gynaecology, however they comprise approximately 2% of all tumours of the gynaecological tract.⁴ Most of them occur in the cervix, but they can also arise in other sites including vulva, vagina, uterus, and ovary.⁵ These tumours are a heterogeneous group of neoplasms that show various histologic findings and biologic behaviours. Neuroendocrine small cell carcinoma is included in the group of high-grade neuroendocrine carcinomas.⁶ Small cell carcinoma, arising in other organs has the same histopathologic characteristics, as the ones originated in the gynaecologic tract. They are also closely resembled to those of small cell lung carcinomas.³ Recent genomic analyses of small cell carcinoma of the lung have revealed potential driver genomic alterations. Some authors believe that the comprehensive genomic characterization of gynaecologic small cell carcinomas may lead to the identification of markers, that result in an improvement of diagnostic reproducibility of small cell carcinomas of the gynaecologic tract and of molecular aberrations, that may be exploited therapeutically in subgroups of the disease. These tumours have an aggressive natural history that is characterized by early

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widespread metastases. The expression of at least one immunohistochemically neuroendocrine marker is a common finding.³ The uterine cervix is the most frequent place in the female genital tract of this cancer and high-risk human papillomavirus (HPV) infection. It seems to play an important role in this development (>90%).⁴ Small cell carcinoma of the vulva is a very rare tumour. Regardless of the location, small cell carcinoma in the gynaecologic tract displays an aggressive clinical behaviour, with few-reported long-term survivors.³ Regional lymph nodes may be involved. This tumour has been observed in women with vulvar intraepithelial neoplasia or squamous cell carcinoma. The small-cell carcinomas of the vagina and vulva need to be distinguished from Merkel cell cancers, a neuroendocrine carcinoma of the skin. Both

tumour types demonstrate neurosecretory granules and have an aggressive clinical course. Attention to the histologic features of neuroendocrine differentiation and the immunohistochemical staining of neuroendocrine markers is necessary to reach a correct diagnosis.⁷ Microscopically, they are composed of small, oval-spindle cells, which are arranged like a sheet, trabecular

or nested pattern. Rosette-like or acinar formation may be seen. The cells have high nuclear to cytoplasmic ratio, scanty cytoplasm, and hyperchromatic nuclei with inconspicuous nucleoli. Nuclear moldings are common. Mitotic figures are numerous with karyorrhectic debris. Crush artefact, nuclear fragmentation and necrosis are frequent. Lymphatic and/or vascular invasion

is often identified. The mitotic activity is frequent. Geographic and comedo-necrosis are frequent. Small foci of squamous and/or glandular differentiation can be seen but they usually are less than 5-10% of the total volume of the tumour.⁵ Immunohistochemistry: neuroendocrine differentiation can be proved with neuroendocrine markers, such as, chromogranin's, synaptophysin, CD56, CD57, neuron specific enolase, protein gene product 9.5 and synaptic vesicle protein 2. These markers recognize antigens that are expressed independently of the specific hormones secreted by neuroendocrine cells. However, not all of the previously listed markers are specific to NETs. Chromogranin-A, synaptophysin and CD56 are the most commonly used neuroendocrine markers in most practices. The demonstration of chromogranin positivity is a diagnostic of a neuroendocrine tumour.⁵ Reactivity for neuron-specific enolase and CD56 is usually present,⁶ although it is known to be a less specific neuroendocrine marker, compared to chromogranin and synaptophysin. The frequent coexistence of neuroendocrine carcinoma and epithelial tumours altogether with the monoclonality of the two components implies a common cellular origin of the neuroendocrine and epithelial components.

The prognosis is related to a tumour size and stage.¹ Better survival is associated with fewer genetic aberrations, but tumour-related mortality occurs in approximately one-third of patients. Regional lymph node and distant metastasis may be present at diagnosis or occur later. The primary treatment for localized tumours is a wide local excision. Regional lymphadenectomy may be included.⁶ The therapy includes surgery, radiotherapy and chemotherapy.

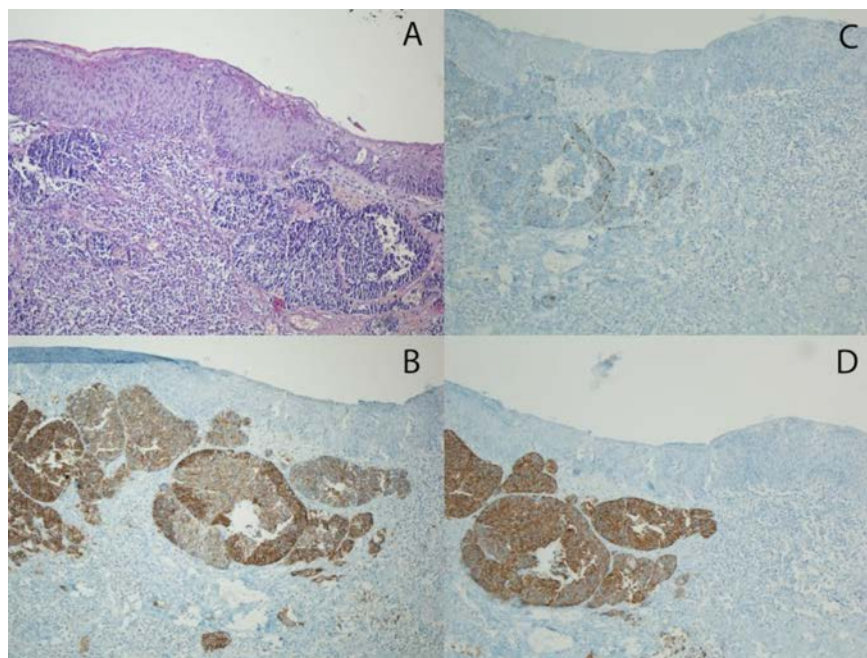


Figure 1. Vulvectomy - Small cell carcinoma markers. A) H&E x10; B) CD56 x10; C) chromogranin A x10; D) synaptophysin x10.

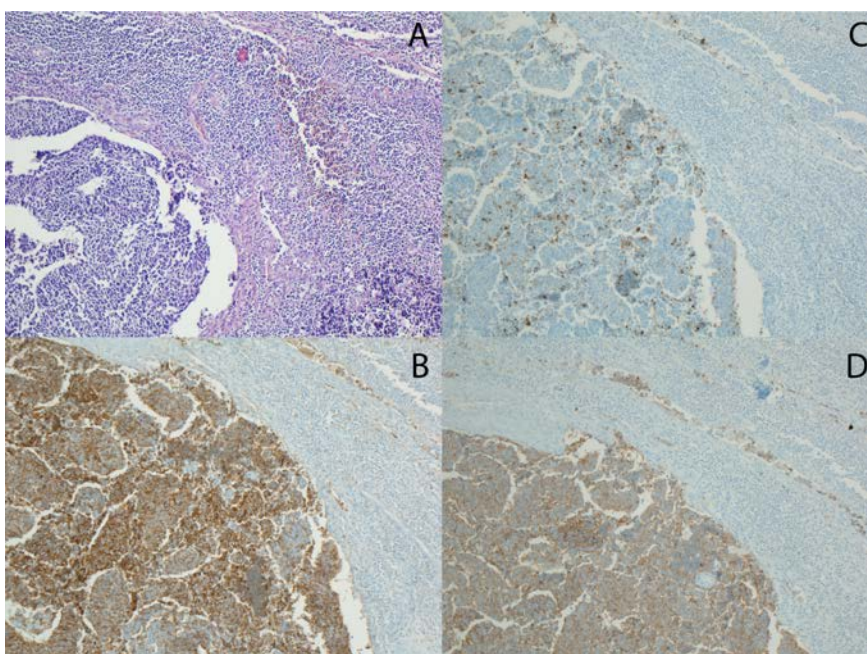


Figure 2. Solid metastasis of neuroendocrine carcinoma small cell in inguinal node. A) H&E x10; B) CD56 x10; C) chromogranin A x10; D) synaptophysin x10.

Conclusions

Neuroendocrine tumours show highly aggressive clinical behaviour, regardless of the site of origin.⁴ Despite the potential differences in etiology and risk factors, small cell carcinoma from different sites of the gynaecologic tract, have similar morphologic appearances and clinical behaviour. They are rare and carry out a poor prognosis. Stage is an important prognostic factor in these tumours. Early stage disease has varied treatment approaches, based on the site of malignancy, but systemic chemotherapy with or without radiation, plays a role in the adjuvant setting to mitigate the risk of recurrence.⁸ Similar to small-cell cancers arising in other sites, it appears that the regional therapy is not a sufficient treatment, for this tumour.

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