Small cell neuroendocrine carcinoma: a case study in gynaecologic cytopathology

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ABSTRACT

The present study shows the case of a 62 years old woman, whose only clinical data was a suspected cervical sarcoma. A liquid-based cytology and biopsies from the cervix and the endometrium were done and sent for diagnostic laboratory.

The cytology showed numerous groups of a variable number of monotonous, small and round cells, having scarce cytoplasm in a diathesis background. The nuclei featured molding, hyperchromasia, “salt-and-pepper” chromatin and no nucleoli. Similar observations could be found with the biopsies, where atypical gland-like groups were also detected.

This neoplasia showed positive immunostaining for neuron specific enolase, synaptophysin and cytokeratin (AE1/AE3 clone antibodies), and a proliferative activity demonstrated by the nuclear marker Ki67/Mib1 immunorreactivity.

The cytological, histological and imunohistochemical findings were consistent with the diagnosis of a small cell neuroendocrine carcinoma. Of all the cervical tumors, this sort of malignancy is one of the rarest and has a very aggressive behavior, with poor prognosis and without effective treatment. Its cause may be related to the Human Papillomavirus infection, but this still remains in study.

Key-words: Colpocytology; Small Cell Neuroendocrine Carcinoma

BACKGROUND

The following case concerns a 63 year old woman, whose clinical condition was suspected to be cervical sarcoma. In order to reach a final anatomical-pathology diagnosis, a liquid-based gynaecological cytology was sent to the Anatomical Pathology Unit, together with biopsies of the cervix and the endometrium.

The colpocytology was processed using the *ThinPrep*® 5000 equipment and stained with the *Papanicolaou* method. The biopsy was processed, and some histological paraffin sections were performed before proceeding to the hematoxylin and eosin staining method, as well as to an immunohistochemical study.

Upon the microscopic observation with low magnification, it was possible to identify, in a diathesis background, multiple groups with different amounts of small-sized and round-shaped cells, and no presence of epithelial cells that might be considered normal (**Fig.1**).

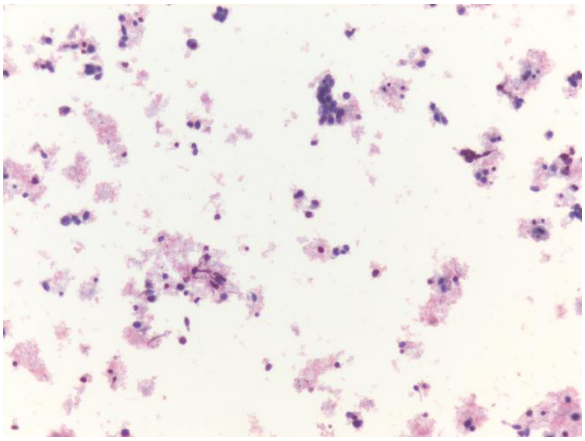

Fig.1 – Global aspect of the cytological slide (*ThinPrep*, *Papanicolaou*, 10x).

When increasing the magnification, it was observed that the referred groups presented cells with scarce cytoplasm, hyperchromatic and round/oval-shaped nuclei possessing relatively constant size among themselves, with nuclear molding and no nucleoli. In its turn, the chromatin had a dotted, delicate and well-distributed pattern (**Fig.2**). Punctual cellular stretching was also observed, suggestive of crushing artifact.

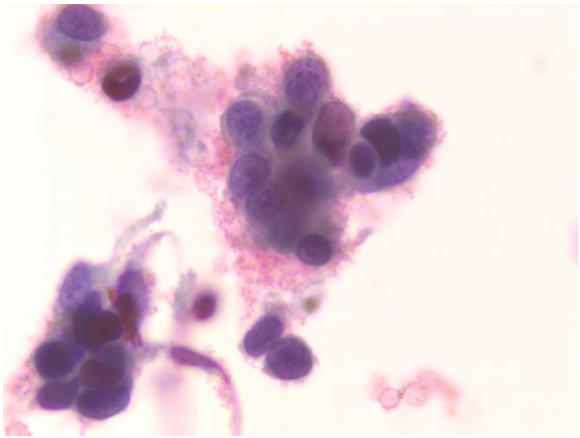

Fig.2 – Atypical cellular group (*ThinPrep*, *Papanicolaou*, 63x).

INITIAL DIAGNOSIS

According to the aforementioned cytological characteristics, there were criteria suggestive of small-cell carcinoma[1-7].

ANALYSIS AND DISCUSSION

Upon the first microscopic observation with low magnification, the cytological findings – **Fig.1** – could be interpreted as the atrophic pattern expected in a 63 year old woman, due to the non-existence of squamous mature cells and the presence of granular material in the background[5]. However, the high cellularity, not always common in atrophy, could be a predictor of an inflammatory process (for instance, chronic cervicitis), susceptible of increasing the amount of small-rounded exfoliated cells (for instance, lymphocytes), or other pathological process.

There were found groups with high cellular density, in a configuration suggestive of tridimensionality, with nuclei on the edges, simulating *feathering* (**Fig.3**). This pattern resembles the traditional groups of adenocarcinoma *in situ*, which could suggest the presence of a concomitant glandular lesion. These groups were also found in the biopsies, being described as *«glanduliform structures with atypical characteristics»*. Specialized publications talk about these adenomatosed components as occurring in parallel, what seems to improve the

prognostic of the original neoplasia[6]. Still, the presence of diathesis is not an indication of adenocarcinoma *in situ*[5].

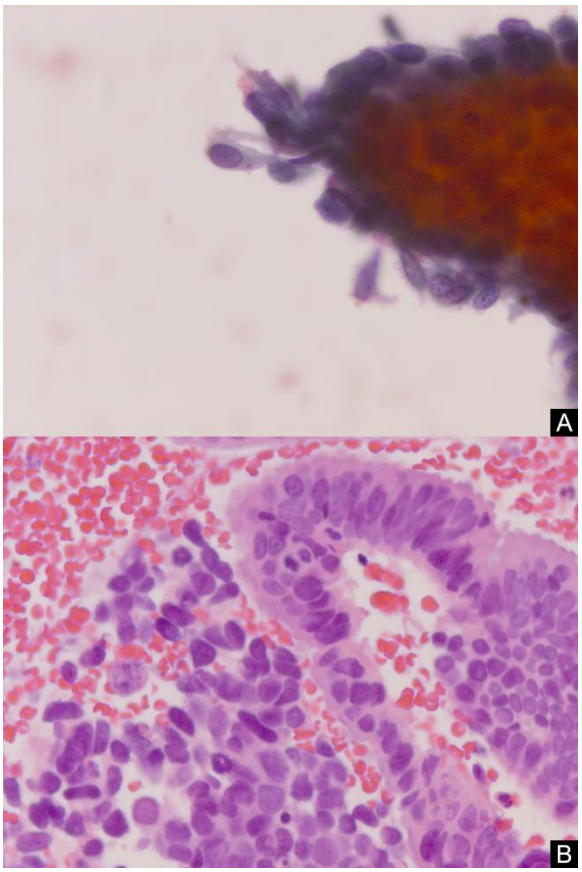

Fig.3 – Glanduliform structures with atypical characteristics: A) Group resembling a glandular atypia (*ThinPrep, Papanicolaou*, 63x); B) Histological image (Hematoxylin-Eosin, 40x).

The absence of orangeophile cells and exuberant pleomorphism prevented a diagnosis of squamous-cell carcinoma, in any differentiation state[5]. At the same time, the inexistence of nuclei with sinuous membrane and the presence of cells attached to each other and not displayed in sheets was decisive to exclude the hypothesis of lymphoma[1]. The criteria to diagnose sarcoma of the endometrium are different from the criteria regarding small-cell carcinoma, and in this case there was at least one cytological group which seemed to sustain this neoplasia[5] (**Fig.4**). As mentioned by scientific publications, it presented cells with low amount of cytoplasm with fusiform aspect, as well as low-dense chromatin with an intense *debris*[8].

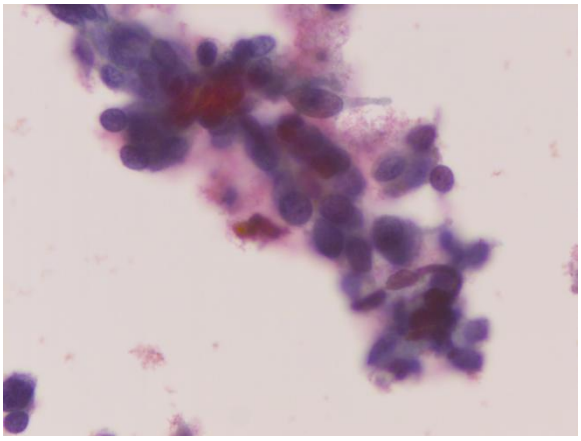

Fig.4 – Cellular group presenting sarcomatosis appearance and a chromatin sample of neuroendocrine type (*ThinPrep, Papanicolaou*, 63x).

Quoting the microscopic description of the biopsies, this case consisted in *«a neoplasia constituted by cells (...) with increased nucleus-cytoplasmic ratio and unnoticeable cytoplasm, hyperchromatic nuclei with molding outlines and (...) necrotic areas observed»* (**Fig.5**). All of this was overlapped by the cytological findings.

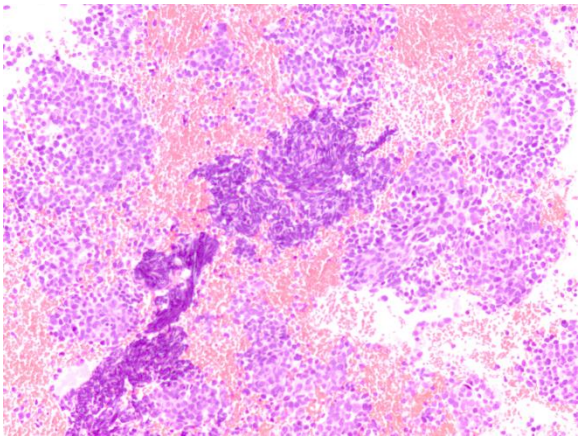

Fig.5 – Endometrium biopsy (Hematoxylin-Eosin, 10x)..

Both samples presented an infiltration of atypical and monotonous cells, with nuclear molding, indistinct nucleoli and “salt-and-pepper chromatin”[4,6] (**Fig.6**). It was acknowledged that the tumour cells were fragile due to the fact that they contained a crushing artifact, with some focuses on the cytological sample and extensions in the histological, similar to the ones in **Fig.7** and as it was expected according to

sources[1,7]. Consequently, considering all the information presented so far, an immunohistochemical study was conducted, with the purpose of making a differential diagnosis with other small-cell neoplasias (such as lymphoma and sarcoma)[9].

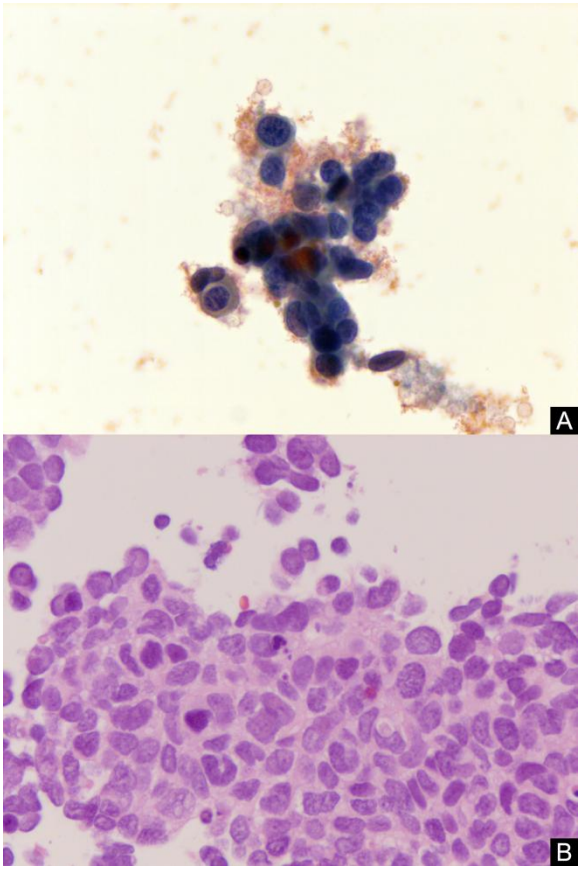

Fig.6 – Chromatin pattern: A) Cellular group of the cytological slide (*ThinPrep, Papanicolaou*, 40x); B) Histological Image (Hematoxylin-Eosin, 40x).

A panel was built, which included epithelial, mesenchymal, neuroendocrine, lymphocytic and other markers like melanocytic, whose results are presented in **Table 1**. The result of the immunohistochemical analysis was positive for neuron-specific enolase, as well as for the synaptophysin and cytokeratin (AE1/AE3 clones), and the proliferative activity, estimated upon the binomial Ki67/Mib1, was considered elevated (75%).

Specialized publications report that more than 80% of the small-cell carcinomas firstly identified through the Hematoxylin-Eosin staining method later become positive for neuroendocrine markers, and for this reason a small-cell carcinoma on the cervix is usually associated with a neuroendocrine neoplasia[9,10].

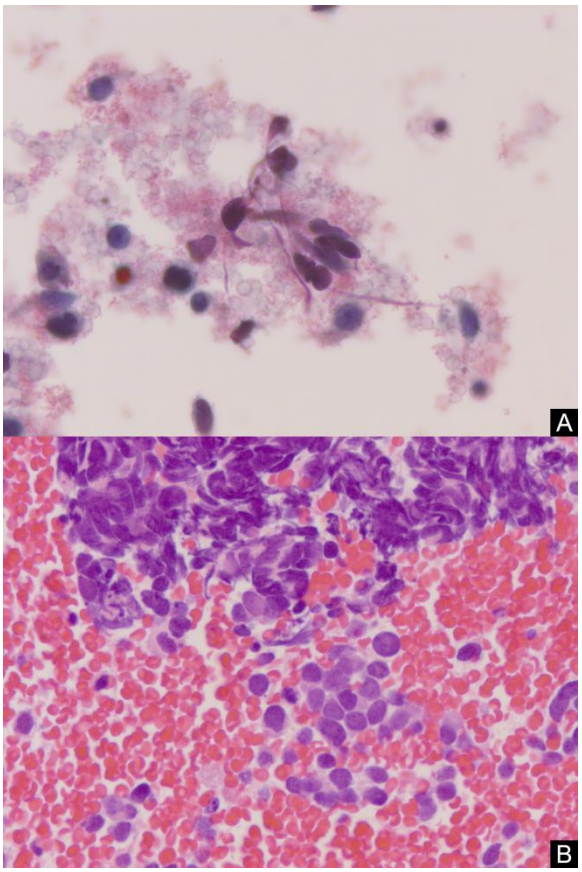

Fig.7 – Crushing artifact: A) Cellular group of the cytological slide (*ThinPrep, Papanicolaou*, 63x); B) Histological image (Hematoxylin-Eosin, 40x).

Furthermore, while the small-cell the variant of squamous carcinoma (which also makes differential diagnosis) can be completely negative for neuroendocrine markers, the small-cell neuroendocrine carcinomas may present variable positivity for cytokeratins, whose expression is useful to exclude other small, blue cell tumours, such as lymphoma and sarcoma[3,4].

After excluding the clinical suspicion, it was proven that the malignant cells had an epithelial expression, having also identified the cytokeratins of more differentiated epithelial components as the atypical glanduliform focuses.

Table 1 – Results of the immunohistochemical assays on the neoplasia

Marker	Marking of Neoplastic cells
Neuron Specific Enolase (NSE)	Intense and diffuse
Synaptophysin	Intense and diffuse
Pan Cytokeratins (AE1/AE3 clones)	Intense and diffuse
Cytokeratins 8/18	Intense and diffuse
Vimentin	Mild
Desmin	Mild and focal
Chromogramine A	Mild and focal
Smooth Muscle Actin	Absence of immunoreactivity
CD10	Absence of immunoreactivity
CD99	Absence of immunoreactivity
Melan A	Absence of immunoreactivity
Ki67/Mib1	75%

CONCLUSION

The immunohistochemical profile of this case corroborated the neuroendocrine differentiation of the neoplasia, initially acknowledged in the cytology. This led to a diagnosis of small-cell neuroendocrine carcinoma.

It should be mentioned that the female reproductive system contains cells of the diffuse neuroendocrine system, and that the neuroendocrine tumours consist in a spectre of malignancies derived from those essentially small cells[4,9].

According to the literature, it is common to regard the occurrence of bulging masses on the cervix, as well as vaginal discharge, as predictors of small cervical cell carcinomas, even if its manifestation is not imperative[4,6,9]. This type of neoplasia can also provoke hormonal changes, unless it has a neuroendocrine differentiation[6].

This condition is especially relevant due to its rarity on the female genitalia. Although numbers vary between studies, it constitutes less than 10% of all the cervical tumours[2,9-11]. This neoplasia has a very aggressive behaviour, and manifests itself by high mitotic index and extensive necrosis[9].

Early metastasis (by lymphatic/hematologic ways) is frequent, especially to the bone, lungs or lymphatic nodes, and it is associated with low cure and high reoccurrence rates[2,6,9]. There is no consensus on the therapeutic that should be applied to these cases, although a combination of radiotherapy and chemotherapy can be regarded as a valid treatment, still not being totally effective[2,3,9,10]. Brain radiation therapy was proposed as a prophylactic measure, similarly to what happens with this type of neoplasia affecting the lungs, with the purpose of reducing beforehand the spreading of metastasis to the brain[10-12]. Other studies suggest potential treatments through therapy addressing HER2+ tumours or the resource to adhesion molecules as a target[2,9].

Finally, the association with the Human Papilloma Virus has been studied, with the existence of some research evidencing the expression of viral particles, and subsequently raising the possibility that this cervical carcinoma's aetiology might differ from its pulmonary homonymous, even if there is no consensus on this isue[1,5,11,13-15].

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