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Atypical stromal cells as a diagnostic pitfall in lesions of the lower female genital tract and uterus: a review and presentation of some unusual cases

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RESUMEN

Antecedentes: las células estromales atípicas (CEAts) en el conducto genital femenino son un hallazgo poco frecuente en lesiones polipoides de vulva, vagina, cuello uterino y endometrio, lo que con frecuencia genera errores diagnósticos.
Objetivo: mostrar los hallazgos de 12 casos enviados a consulta por la sospecha de una lesión maligna.
Material y métodos: estudio clínico-patológico de 12 casos con inmunohistoquímica de actina, desmina, S100, Ki67, RE y RP.
Resultados: las células estromales atípicas se encontraron en un patrón multifocal, en tres casos de lesiones de vulva (incluido un caso de liquen escleroso), dos pólipos vaginales, dos casos de cuello uterino, incluido uno prolapsado y un carcinoma escamoso y, por último, cuatro casos de pólipos endometriales y un caso de adenomiosis. Los marcadores de inmunohistoquímica en las células estromales atípicas fueron positivos para receptores hormonales de estrógenos y progesterona y sólo focalmente para actina. El índice de proliferación Ki67 fue bajo.
Conclusiones: las células estromales atípicas son reactivas no específicas o degenerativas, con un índice de proliferación muy bajo con receptores hormonales y capacidad para expresar marcadores de músculo liso y de estroma endometrial. Presentamos casos, hasta ahora no publicados, de células estromales atípicas asociadas a un liquen escleroso en la vulva, un carcinoma escamoso del cuello uterino y un cuello uterino prolapsado. Se plantean además, como diagnósticos diferenciales, sitio de implantación exagerado y nevo azul, ya que las células trofoblásticas y névicas presentan características similares a las células estromales atípicas.
Palabras clave: células estromales atípicas, conducto genital femenino, útero.

ABSTRACT

Background: Atypical stromal cells of the female genital tract represent a potential diagnostic pitfall in biopsy material and are a relatively uncommon finding in polypoid lesions of the vulva, vagina, cervix and endometrium.
Objective: To report the pathological findings of 12 such cases who were sent in consultation with a presumptive diagnosis of malignancy.
Material and methods: Clinicopathological review of 12 cases with immunohistochemical study of actin, desmin, S100, Ki67, ER and PR.
Results: Atypical stromal cells were found in a multifocal pattern in three cases of vulval lesions (including one case of lichen sclerosus), 2 vaginal polyps, 2 cervical cases which included one prolapsed cervix and a squamous cell carcinoma and finally, 4 cases of endometrial polyps and one case of adenomyosis. Immunohistochemically, the atypical stromal cells were positive for ER, PgR but only focally for actin. Their Ki67 index was low.
Conclusions: Atypical stromal cells are non-specific reactive or degenerative with a very low proliferation index that have hormonal receptors and capacity to express both smooth muscle and endometrial stromal markers. We present hitherto unreported cases of ASCs in association with vulval lichen sclerosus, squamous cell carcinoma in cervix and prolapsed cervix. Further differential diagnoses with cervical exaggerated implantation site and cervical blue nevi are emphasized since both trophoblastic and naevic cells exhibit similar nuclear features.
Key words: uterus, cervix, vagina, vulva, atypical stromal cells, bizarre cells.

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Atypical stromal cells (ASCs) of the female genital tract are a relatively uncommon finding in various polypoid lesions of the vulva, vagina, cervix and endometrium.[1] Similar cells are also reported in the stroma of fibroepithelial polyps and the normal mucosa of the anus.[2]

Atypical stromal cells are stellate, enlarged cells with moderate to severely atypical hyperchromatic, multilobulated nuclei with little proliferative activity and no mitoses. Their chromatin is dense often with prominent nucleoli exhibiting frequent cytoplasmic pseudoinclusions. Morphologically similar cells can be found in the thin myxoid subepithelial layer that extends from the cervix to the vulva.[3] Atypical stromal cells are associated with a benign behaviour, but represent a potential diagnostic hazard as they are often misinterpreted as a malignant feature. This paper reviews the current knowledge and clinicopathological findings of 12 such cases that were sent in consultation with a presumptive diagnosis of malignancy to one of the authors (FFN).

SIGNIFICANCE AND HISTOGENESIS

Atypical stromal cells of the lower female genital tract were first described by Norris and Taylor[4] in fibroepithelial stromal polyps of the vagina. They noted that these lesions contained atypical stromal cells and emphasized their differential diagnosis with malignant mesenchymal vaginal neoplasms.[5]

The benign behaviour of atypical stromal cells has been repeatedly confirmed,[6] but their aetiology is still unclear: some authors[3] have proposed that they are related to the primitive stem cell population present in the thin myxoid subepithelial layer of lower female genital tract, representing some mesenchymal cells which have the ability to differentiate towards either smooth muscle or a müllerian stromal lineage. However, this hypothesis would not explain the presence of these cells in endometrial lesions. Primitive mesenchymal (stem?) cells may eventually proliferate as a response to an unknown stimulus, ultimately undergoing reactive or degenerative phenomena.[5,7]

In order to explain the pathogenesis of their phenotype, several alternatives have been considered:

1. Mast cells seem to display a relationship with atypical stromal cells present in vaginal polyps and normal anal mucosa. Consequently, it has been suggested[2] that they may play a role in the formation of multinucleated stromal cells, as these cells are known to be essential to the development of inflammation, fibrosis and angiogenesis.
2. A peripheral nerve sheath origin of the atypical stromal cells has also been proposed[8] on the basis of some of their optic and electronmicroscopical features, which include pseudo-inclusions, nuclear multilobulation, thin cytoplasmic process, intracellular filaments and the additional positivity for S-100, similar to those found in Schwann cells.
3. Atypical stromal cells may have either a smooth muscle or an endometrial stromal immunophenotype,[1] a similar phenomenon that occurs in mixed stromal uterine tumors that are composed of both endometrial and smooth muscle cells. Atypical stromal cells display positivity for oestrogen receptors;[3] however, hormonal status does not appear to play a seemingly aetiological role nor in their genesis neither in their evolution.[1]

INTERPRETATION PROBLEMS AND DIFFERENTIAL DIAGNOSES

Misdiagnosis of malignancy represents the main point of interest in these cases; to exemplify this, it is worth analyzing a series of 15 endometrial specimens containing atypical stromal cells that were sent in consultation,[7] specifically because of their initial histopathological diagnoses, which were: malignant mixed mesodermal tumour, adenosarcoma, dysplastic endometrial polyp, endometrial polyp with clusters of atypical trophoblastic cells and endometrial stromal sarcoma and atypical macrophages. In the endometrium, it is worth emphasizing that atypical stromal cells can be found in tissue from fragmented endometrial biopsy specimens, thus complicating an already difficult differential diagnosis.[1]

A review of the literature (table 1) shows the various differential diagnoses considered in different areas of the lower female genital tract and endometrium, including a non-polypoid proliferative endometrium.[1] We would add to them new differential diagnoses with both cervical exaggerated implantation site[9] and cervical blue naevi, since trophoblastic and naevic cells exhibit similar nuclear features.

Table 1. Differential diagnoses of atypical stromal cells in specific female genital tract sites

Site	*Differential diagnoses*
Vulva	Fibroepitelial polyps,[11] granulation tissue polyps[6]
Vagina	Rhabdomyoma,[12] fibroepithelial polyps,[6,11] agressive angiomyxoma,[11,13] angiomyofibroblastoma,[11,13] myofibroblastoma,[11] cellular angiofibroma,[13] smooth muscle neoplasms,[14] prepubertal vulval fibroma[13]
Cervix	Adenosarcoma,[15] adenofibroma,[13] sarcoma botryoides,[5] endometrial stromal sarcoma,[5] malignant mixed müllerian tumor,[14] blue nevus (present paper). Microinvasive cells from squamous cell carcinoma (present paper), cervical exaggerated implantation site[9]
Endometrium	Adenomyoma,[15] adenosarcoma,[15] endometrial stromal sarcoma,[14] carcinosarcoma,[1] trophoblastic lesions[7]

IMMUNOHISTOCHEMISTRY OF ATYPICAL STROMAL CELLS

In a review of the literature, neither ultrastructure nor immunohistochemistry seem to throw any light on the identity of atypical stromal cells. However, it must be borne in mind that these immunohistochemical results originate from many different papers using different methodology and published in different epochs, consequently lacking a uniform approach. Cells are invariably positive for vimentin,[1,7,8] oestrogen,[1,6,7] androgen,[7] and progesterone receptors,[1,3,7] occasionally and focally for CD10, a frequent endometrial stroma marker,[7,10] for smooth muscle markers such as actin,[1,10] desmin,[3,6,10] h-caldesmon,[10] and occasionally for S100,[8] a Schwann cell and lipid cell marker. On the other hand, atypical stromal cells are consistently negative for cytokeratins,[1,3] epithelial membrane antigen,[8] myogenin,[1] CD34,[1] α-antitrypsin,[3] antichymotrypsin,[3,8] factor VIII,[8] macrophage markers[3] and lysozyme.[3]

PRESENT SERIES

From the consultation files of the FFN at the Department of Pathology of the University of Granada, Spain, we analyzed atypical stromal cells present in twelve cases of lesions of the lower female genital tract. Most cases were sent in consultation with a diagnosis of malignancy. The bizarre cells exhibited enlarged, multilobulated, often multiple, nuclei with hyperchromatism (figure 1a and b) and had no mitoses. They occurred in small amounts in predominantly sub-epithelial locations with a multifocal pattern (figures 2 and 3); however, they also had a deep localization in the stroma. The lesions were associated with the entities shown in table 2.

It is interesting to note that atypical stromal cells are reported here for the first time in the stroma of lesions such as *vulval lichen sclerosus* (case 3), *cervical squamous cell carcinoma* (figure 4), in which atypical stromal cells were

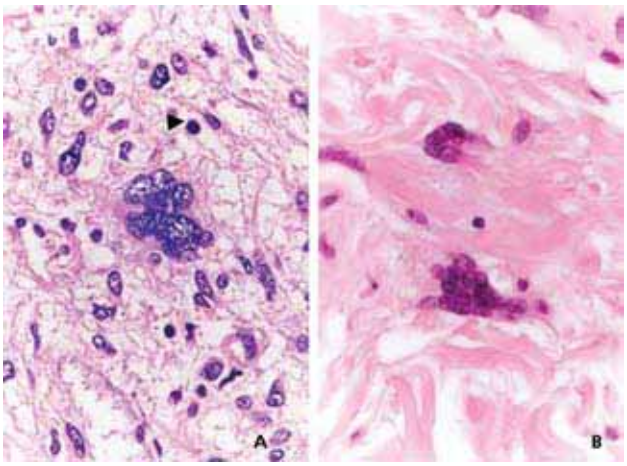

Figure 1. Atypical stromal cells with severely atypical nuclei exhibiting multilobulation (A) and multinucleation (B) in the stroma of an endometrial (A) and vaginal (B) polyps. A mast cell (arrowhead) can be noted in the immediate vicinity.

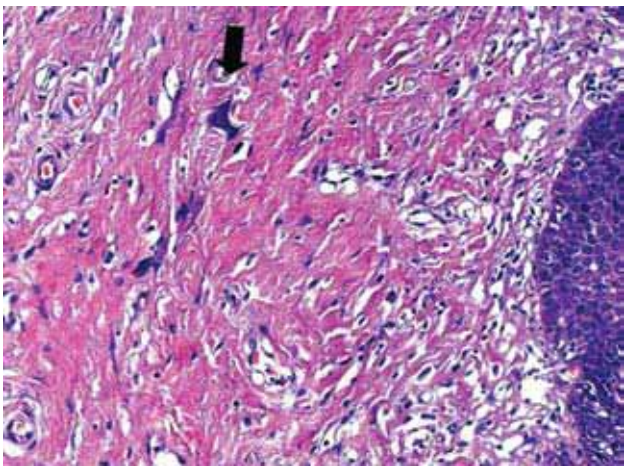

Figure 2. Cervical prolapse in a 51-year-old patient. Large, bizarre, stellate cells are present in the subepithelial stroma (arrow).

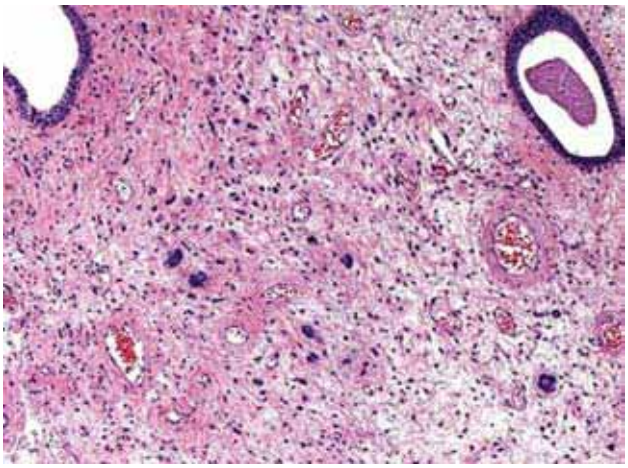

Figure 3. Endometrial polyp in a postmenopausal woman with bizarre stromal cells initially that was originally diagnosed as a sarcomatous change.

Table 2. Initial diagnoses sent on consultation of atypical stromal cells containing lesions in female genital tract

Case	*Site*	*Initial diagnosis*
1	Vulva	Polyp
2	Vulva	Polyp with atypical stromal cells
3	Vulva	Lichen sclerosus et atrophicus
4	Vagina	Polyp with atypical stroma
5	Vagina	Polyp with atypical stroma
6	Cervix	Squamous cell carcinoma with microinvasion
7	Cervix	Atypical stromal cells in prolapsed cervix
8	Endometrium	Polyp with atypical stromal cells
9	Endometrium	Endometrial polyp with atypical stromal cells
10	Endometrium	Polyp
11	Endometrium	Adenomyoma with bizarre cells
12	Endometrium	Polyp and sarcoma

found in the neighbouring stroma and simulated singe cell stromal invasion (case 6) and finally, in a *prolapsed, otherwise normal cervix* (case 7).

Immunohistochemistry (table 3) showed constant positivity for oestrogen and progesterone receptors but only isolated, focal, positivity for actin (figure 5a) and desmin. Based on these findings it is difficult to ascribe a myofibroblastic origin for atypical stromal cells. It is clear, however, that the previously unreported Ki-67 index in these lesions (figure 5b) was extremely low in the atypical stromal cells, revealing their low proliferative capacity and supporting a reactive or degenerative origin.

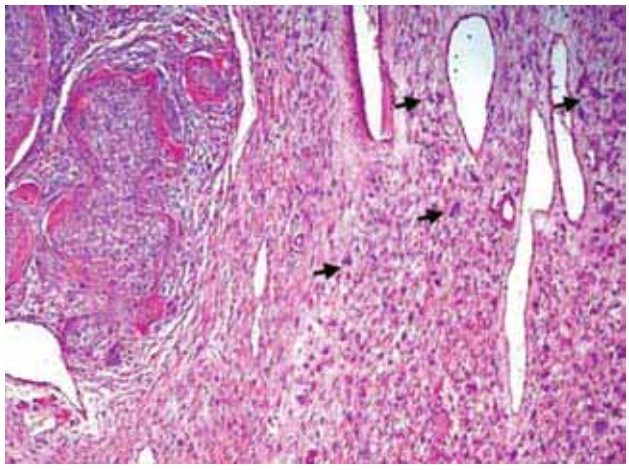

Figure 4. Cervical squamous cell carcinoma with bizarre cells in the stroma (arrows) simulating microinvasion.

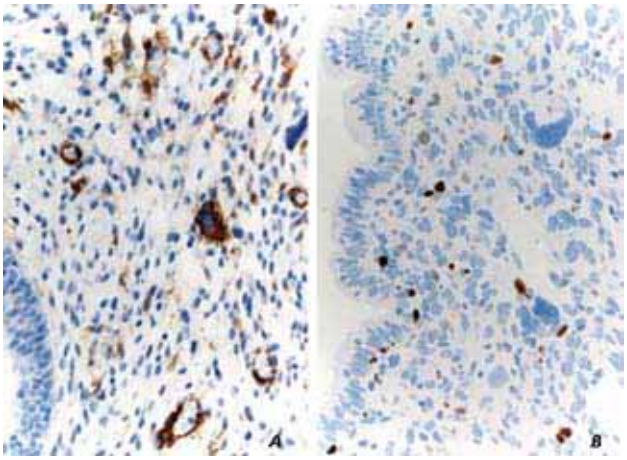

Figure 5. Immunohistochemistry. Occasional positivity for actin (A). Ki 67 index is very low in bizarre cells (B).

Table 3. Immunohistochemical findings in atypical stromal cells containing lesions in female genital tract

Case	*ER*	*PgR*	*Actin*	*Desmin*	*S100*	*K167*
2	+	+	NA	-	NA	NA
3	+	+	+ focal	+	-	< 10%
4	NA	NA	-	+ focal	-	NA
5	+	+	-	NA	-	< 10%
6	-	-	-	-	-	< 10%
7	+	+	-	-	-	-
9	NA	NA	-	NA	NA	NA
10	NA	NA	-	NA	-	NA
11	+	+	NA	-	-	-
12	+	+	-	NA	NA	< 10%

NA: tissue not available.

CONCLUSIONS

In our opinion, the frequent subepithelial situation of the atypical stromal cells and their heterogeneous cytostructural and immunohistochemical features point towards an origin from mesenchymal (stem?) cells present during the development of foetal lower genital tract and presumably uterus, that are capable of exhibiting a smooth muscle or an endometrial stromal phenotype. Atypical stromal cells are probably reactive or degenerative stromal cells with a very low proliferation index that somehow keep hormonal nuclear receptors. Immunohistochemical findings, with only isolated and inconstant positivity for actin and other smooth muscle markers do not necessarily confirm a myofibroblastic origin.

While atypical stromal cells now pose few problems in the diagnosis of lesions of the vagina, where they are well recognized lesions, they create however some difficulty in the interpretation of cervical and even more so, in endometrial biopsies, where they represent a unusual and unexpected finding. This fact, jointly with the scarce tissue available in endometrial biopsy, may induce differential diagnoses with adenosarcoma, atypical trophoblastic cells and stromal sarcoma.

Atypical stromal cells may be present in the stroma of squamous cell carcinoma of cervix, where they have a reactive nature and should be differentiated from invasive cells, particularly based on their negativity for epithelial markers.

REFERENCES

1. Lo Monaco M, Puzzo L, Brancato F, Torrisi A, Magro G. Endometrial atypical (bizarre) stromal cells: a potential diagnostic pitfall in biopsy. Pathol Res Pract 2004;200:625-30.
2. Groisman GM, Polak-Charcon S. Fibroepithelial polyps of the anus: a histologic, immunohistochemical, and ultrastructural study, including comparison with the normal anal subepithelial layer. Am J Surg Pathol 1998;22:70-76.
3. Hartmann CA, Sperling M, Stein H. So-called fibroepithelial polyps of the vagina exhibiting a unusual but uniform antigen profile characterized by expression of desmin and steroid hormone receptors but no muscle-specific actin or macrophage markers. Am J Clin Pathol 1990;93:604-8.
4. Norris HJ, Taylor HB. Polyps of the vagina. A benign lesion resembling sarcoma botryoides. Cancer 1966;19:227-32.
5. Nucci MR, Young RH, Fletcher CD. Cellular pseudosarcomatous fibroepithelial stromal polyps of the lower female genital tract: an underrecognized lesion often misdiagnosed as sarcoma. Am J Surg Pathol 2000;24:231-40.
6. Halvorsen TB, Johannesen E. Fibroepithelial polyps of the vagina: are they old granulation tissue polyps? J Clin Pathol 1992;45:235-40.
7. Tai LH, Tavassoli FA. Endometrial polyps with atypical (bizarre) stromal cells. Am J Surg Pathol 2002;26:505-9.
8. Metze K, Andrade LA. Atypical stromal giant cells of cervix uteri-evidence of Schwann cell origin. Pathol Res Pract 1991;187:1031-8.
9. Stolnicu S, Radulescu D, González-Rocha T, Timar I, Puscasiu L, Nogales FF. Exaggerated placental site lesion with unusual presentation in the cervix of a perimenopausal patient. APMIS 2008;116:160-2.
10. Usubütün A, Karaman N, Ayhan A, Küçükali T. Atypical endometrial stromal cells related with a polypoid leiomyoma with bizarre nuclei: a case report. Int J Gynecol Pathol 2005;24:352-4.
11. Laskin WB, Fetsch JF, Tavassoli FA. Superficial cervicovaginal myofibroblastoma: fourteen cases of a distinctive mesenchymal tumor arising from the specialized subepithelial stroma of the lower female genital tract. Hum Pathol 2001;32:715-25.
12. Miettinen M, Wahlström T, Vesterinen E, Saksela E. Vaginal polyps with pseudosarcomatous features. A clinicopathologic study of seven cases. Cancer 1983;51:1148-51.
13. McCluggage WG. Recent developments in vulvovaginal pathology. Histopathology. 2008 Jul 11. [Epub ahead of print]
14. Chhieng DC, Elgert PA, Cangiarella JF, Cohen JM. Cytology of polypoid adenomyomas: a report of two cases. Diagn Cytopathol 2000;22:176-80.
15. Gilks CB, Clement PB, Hart WR, Young RH. Uterine adenomyomas excluding atypical polypoid adenomyomas and adenomyomas of endocervical type: a clinicopathologic study of 30 cases of an underemphasized lesion that may cause diagnostic problems with brief consideration of adenomyomas of other female genital tract sites. Int J Gynecol Pathol 2000;19:195-205.