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Arias-Stella reaction of the cervix: The enduring diagnostic challenge

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Summary

Background: The Arias-Stella reaction is a hormone-related atypical endometrial change characterized by hypertrophy and vacuolization of glandular epithelial cells, associated with marked nuclear pleomorphism, enlargement, and hyperchromasia. When presenting in extra-uterine sites, the differentiation of Arias-Stella changes from other more ominous clear cell lesions may pose significant difficulties.

Case Report: We report a case of an endocervical clear cell lesion incidentally discovered during a prenatal visit of a young pregnant woman. Interpretation of the pathological findings was complicated by the small size and fragmentation of the specimen.

Conclusions: Recognition of Arias-Stella reaction in extra-uterine sites, especially in young women, is critical to avoid misdiagnosis of this innocuous lesion as clear cell adenocarcinoma. Attention to cellular and nuclear detail, as well as careful consideration of the clinical scenario, is crucial for establishment of the correct diagnosis.

key words: **Arias-Stella • clear cell carcinoma • endocervix**

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Background

The Arias-Stella phenomenon was first described by Javier Arias-Stella in 1954 as atypical endometrial changes associated with the presence of chorionic tissue [1]. The characteristic histologic features of the Arias-Stella reaction include large cells with abundant eosinophilic or vacuolated cytoplasm, nuclear enlargement, and hyperchromasia [2]. The appearance of the hypertrophic nuclei may vary widely from round or ovoid nuclei with a vesicular chromatin pattern to irregular nuclei with a compact, pyknotic pattern. Some variants exhibit prominent intranuclear cytoplasmic invaginations or pseudoinclusions. The nuclei may protrude into the glandular lumen creating a "hobnail" appearance. There may be loss of cell polarity with papillary projections and epithelial tufting. Mitotic activity is usually absent [2].

Originally described in the uterine endometrium, the Arias-Stella reaction has subsequently been documented outside of the uterine corpus, including fallopian tube, vagina, inclusion cysts of the ovary, paraovarian and paratubal cysts, and mucinous cystadenoma [2], as well as in foci of endometriosis (peritoneum, subcutis, umbilicus, bladder wall) [3].

In addition to these sites, the Arias-Stella reaction may occur in the endocervix [4–6], including within endocervical polyps [7,8]. In spite of various additional reports and a recent excellent review that illustrates the wide spectrum of histologic features of Arias-Stella reaction in the endocervix [6], this lesion continues to pose diagnostic difficulties, as suggested by the relative frequency with which these cases are submitted to our consultation service.

Indeed, the extreme nuclear and cellular atypia of the Arias-Stella reaction, even though classically described, may elude even the experienced pathologist. When assessing clear cell lesions of the genital tract, awareness of the clinical context is critical in establishing a diagnosis, in particular when the changes occur in extra-uterine sites and biopsy material is limited. Arias-Stella changes are virtually limited to conditions associated with hormonal stimulation, either from endogenous or exogenous sources. Arias-Stella reaction may be encountered during normal or ectopic pregnancy, in gestational trophoblastic disease, or in association with exogenous hormone administration. In this report, we describe a case of Arias-Stella changes in the endocervix of a pregnant 37-year-old woman and reiterate the importance of accurately diagnosing endocervical clear cell lesions, particularly in young women where misdiagnosis may have especially grave consequences.

Case Report

The patient is a 37-year-old G2P1 pregnant woman who had an uneventful first-trimester pregnancy course. During a routine prenatal examination at 10 weeks' gestation, subtle and focal thickening of the endocervical mucosa was noted involving an area measuring less than 1 cm in greatest dimension. There was no associated mass effect. A cervical biopsy was performed. The remainder of the pregnancy proceeded normally and resulted in the uncomplicated delivery of a healthy newborn at full term.

Pathological findings

The cervical wedge biopsy specimen measured 0.5 cm in greatest dimension and was partially covered by irregular gray-tan epithelium. Histologic examination revealed a focally exuberant proliferation of glandular structures lined by large cells demonstrating prominent clear cell metaplasia and hobnailed luminal protrusions (Figure 1A–C). The nuclei of the atypical glands appeared hyperchromatic and pleomorphic and contained smudged chromatin. Focal nuclear pseudoinclusions were noted (Figure 1C). The interface between atypical glands and underlying stroma was smooth, without evidence of invasion or associated desmoplastic response (Figure 1B). The glands were surrounded by decidualized stromal cells, focally admixed with mononuclear cell infiltrates (Figure 1B). There was no evidence of mitotic activity in the atypical glands.

The amount of relevant material with atypical glandular changes was insufficient for a detailed or extensive immunohistochemical work-up. At the originating institution stains for estrogen receptor (ER), progesterone receptor (PR), and p16 were performed. The results of these stains within the lesional glands were scored as "indeterminate" based on the low quantity of affected tissue available for analysis. Adjacent to the regions involved by Arias-Stella changes, normal appearing glandular epithelium and decidual cells showed positivity for ER, suggestive of endometrial differentiation (Figure 1D).

Discussion

We described a case of an endocervical lesion with clear cell features, incidentally detected during routine prenatal examination of a gravid patient. The histopathologic analysis of this lesion was compromised by the small size and disruption of the biopsy sample. Despite these limitations, a diagnosis of Arias-Stella reaction could be established with confidence, based on the following constellation of clinical and pathological factors. First, as is typical for the Arias-Stella reaction, atypical glands were only focally present, and were interspersed with normal appearing glands. Second, there was striking nuclear pleomorphism, with conspicuous variation in nuclear changes between cells. Third, in spite of this marked degree of nuclear pleomorphism and hyperchromasia there was no mitotic activity in the atypical glands, which showed smudgy, degenerative/regenerative nuclear changes as well as nuclear pseudoinclusions. Fourth, the interface between the atypical glands and subjacent stroma was smooth and did not show evidence of a desmoplastic reaction. Finally, as evidenced by the decidualization of the surrounding stromal cells and confirmed by the clinical history of pregnancy, the morphologic changes occurred in the context of hormonal stimulation.

Based on histologic and cytologic criteria, five variants of the Arias-Stella reaction have been described that loosely reflect the phases of normal endometrium and the degree of atypia. Among these, the secretory or hypersecretory pattern is the classically recognized form, characterized by diffuse cytoplasmic vacuolization of the glandular epithelium, associated with enlarged and hyperchromatic nuclei [2]. The large and vacuolated cells are typically intermixed with focally less vacuolated, eosinophilic cells with a dense cytoplasm. The so-called monstrous pattern, characterized

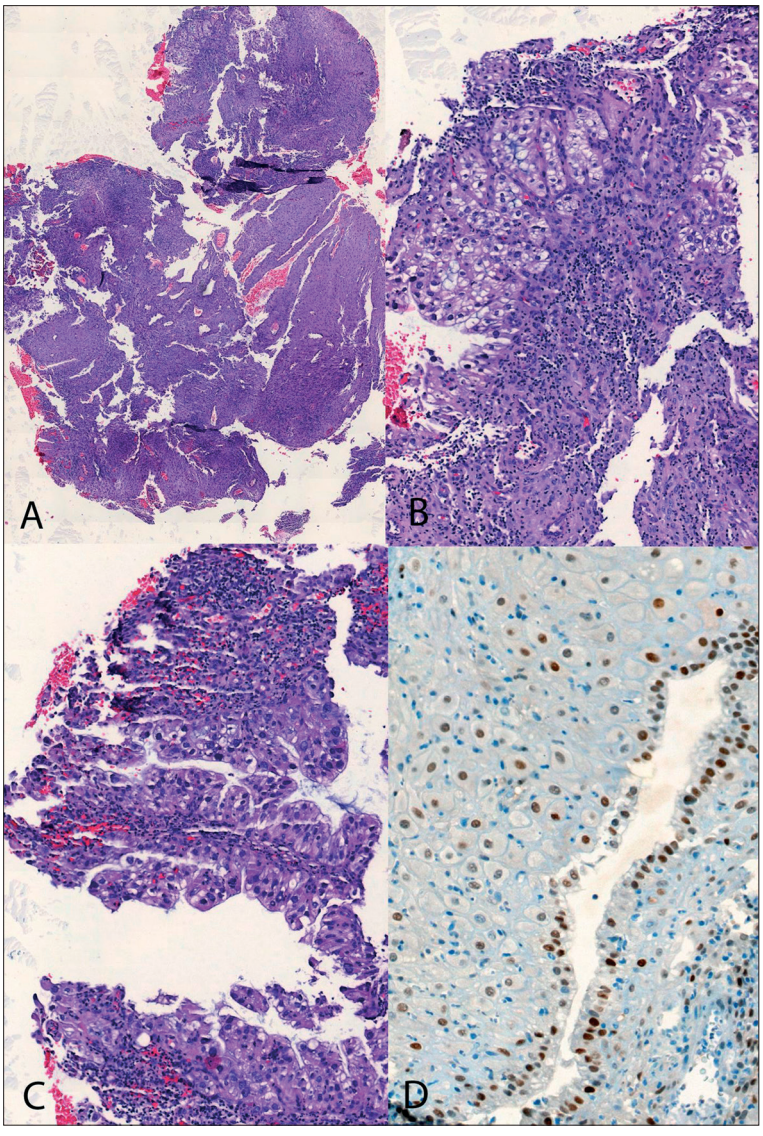

Figure 1. (**A**) Scanning magnification overview of the endocervical biopsy specimen, with evident fragmentation. (**B**) Proliferation of glands lined by markedly enlarged, vacuolated clear cells with enlarged hyperchromatic nuclei (medium power). The border between glands and underlying decidualized stroma is regular without desmoplastic changes. Mononuclear cell infiltrates are noted in the decidua. (**C**) High power view of an area showing glands exhibiting a papillary architecture and lined by cells with more densely eosinophilic cytoplasm. Marked nuclear pleomorphism is seen, as well as several nuclear pseudoinclusions. Mitoses are absent. (**D**) High power view of ER immunohistochemical stain showing positive nuclear staining in glandular epithelium and decidual stromal cells.

by the presence of giant and bizarre nuclei that show frequent pseudoinclusions, is less prevalent but a major source of diagnostic difficulties [2]. As in the current case, the endocervical Arias-Stella reaction frequently shows the monstrous cell pattern, albeit only focally, which further exacerbates its diagnostic challenge.

The differential diagnosis of clear cell lesions in the endocervix revolves mainly around three entities: Arias-Stella reaction, microglandular hyperplasia, and clear cell adenocarcinoma. Endocervical Arias-Stella changes are present, at least focally, in almost 10% of gravid uteri [9,10]. The reaction is usually focal and preferentially located in superficial glands of the proximal cervical canal [9], although more extensive involvement has been described [11]. Overall, the histologic and cytologic features of the Arias-Stella reaction in the endocervix mimic those of the endometrium, including markedly hypertrophic cells with vacuolated or eosinophilic cytoplasm and highly atypical, hyperchromatic nuclei [9,11]. Typically, strikingly pleomorphic cells are interposed between bland, normal-appearing cells. Hobnail patterns are focally present and mitoses are uncommon.

Like Arias-Stella changes, microglandular hyperplasia has been linked to hormonal perturbations, including pregnancy, although more recent epidemiologic studies cast doubt on the validity of those associations [12]. Microglandular hyperplasia is commonly characterized by densely packed and irregularly shaped glands that often show varying degrees of cystic dilation. The cells lining the glands contain mucin and commonly exhibit sub- or supranuclear vacuoles. Mitotic activity is modest. The nuclei in microglandular hyperplasia are generally uniform in size and shape, although focal atypia may be present [11,13]. A hobnail cell pattern may be focally present.

While traditionally linked to *in utero* diethylstilbestrol (DES) exposure, clear cell carcinoma can arise without a history of DES exposure. Clear cell carcinoma is more commonly associated with a mass-forming lesion. At the microscopic level, clear cell carcinoma exhibits an infiltrative growth pattern with an irregular distribution of glands and often has solid or papillary growth patterns. Although it may also display cytoplasmic clearing and similar hobnail cells, in contrast with Arias-Stella reaction, clear cell carcinoma is usually

mitotically active. Furthermore, the spectrum of bland to highly atypical cells characteristic of Arias-Stella reaction is not seen in clear cell carcinoma [11]. One of the major histologic aids in the differential diagnosis between Arias-Stella changes and clear cell carcinoma is the low-power assessment of the growth pattern of the lesion and, in particular, the interface between involved glands and underlying stroma. At low power, the glands of clear cell carcinoma will have an irregular distribution within the stroma, while those of Arias-Stella reaction will more likely conform to the regular distribution of normal endocervical glands. Glands involved by Arias-Stella changes will maintain their border, while clear cell carcinoma will display an irregular border associated with desmoplastic stromal reaction.

Less common tumors or tumor-like lesions of the female genital tract that might enter the differential diagnosis, such as mesonephric hyperplasia, metastatic renal cell carcinoma, steroid cell tumors and others, have been discussed in detail elsewhere [11,14]. The list of differential diagnoses was recently expanded to include clear cell variant of malignant melanoma as an extremely rare malignancy involving the endocervix [15].

In the current case, the history of pregnancy is helpful to establish a diagnosis of Arias-Stella reaction. A history of pregnancy or exogenous hormonal stimulation may not be always be known or provided, but can often be derived from the presence of decidual changes in the surrounding stroma. In addition to pregnancy, Arias-Stella reaction is well known to occur in nonpregnant patients taking various types of hormonal preparations [16]. A recent report of cervical Arias-Stella reaction in a patient taking phytoestrogens highlights the fact that the source of hormonal exposure may not always be immediately evident [17]. Importantly, knowledge that the patient is pregnant or otherwise exposed to hormonal stimulants should not deter one from rendering a diagnosis of clear cell adenocarcinoma, as several cases of endocervical clear cell adenocarcinoma in pregnant women have been reported [18,19].

The diagnosis of Arias-Stella reaction is primarily based on microscopic analysis of routinely hematoxylin-eosin-stained sections. While precluded by the small size of the biopsy at any rate, immunohistochemical studies were unlikely to be of any diagnostic utility in this case, as the value of immunohistochemistry in the differential diagnosis of clear cell lesions of the genital tract, in general, is limited. Vang et al. [20] recently studied the role of immunohistochemistry in distinguishing endometrial Arias-Stella reaction from clear cell carcinoma and found diminished Ki-67 and p53 immunostaining in Arias-Stella reaction compared with clear cell carcinoma, both with respect to composite immunohistochemical scores or overall positivity. The diagnostic value of these findings in individual cases remains to be demonstrated. Staining for ER and PR was of less clinical utility in differentiating Arias-Stella reaction from clear cell carcinoma or other similar malignancies [2,20]. Most studies were performed in the uterine endometrium; the immunophenotype of the Arias-Stella reaction involving the endocervix or other extra-uterine sites remains undetermined.

As in the majority of Arias-Stella reactions, mitotic activity was absent in our case. It needs to be emphasized that the presence of mitoses should not exclude a diagnosis of Arias-Stella changes. Mitoses, including atypical forms, have been well documented in both endometrial and endocervical Arias-Stella reaction [8,21,22]. Conversely, it is important to recognize that a significant proportion of clear cell adenocarcinomas (up to 25%) are devoid of any mitotic activity [20].

The highly atypical cytology associated with the Arias-Stella reaction of endometrium or endocervix may give rise to problems in cytologic interpretation [23,24]. The cytologic features are similar to the histologic appearance [24]. Clues to the diagnosis include a relative preservation of the nuclear/cytoplasmic ratio, fine chromatin pattern, and presence of nuclear grooves and inclusions. There is great cytological overlap between the Arias-Stella reaction and adenocarcinoma, therefore caution is warranted when making a diagnosis of adenocarcinoma in younger, child-bearing women based on cytology [23–25].

Conclusions

In summary, we presented a case of endocervical Arias-Stella reaction, incidentally discovered in a pregnant patient. Recognition of Arias-Stella reaction in extra-uterine sites, especially in young women, is critical to avoid misdiagnosis of this innocuous lesion as clear cell adenocarcinoma. Especially when dealing with small and fragmented biopsy specimens, attention to cellular and nuclear detail and awareness of the clinical context (pregnancy or other forms of hormonal stimulation) are crucial.

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