

Pseudo-tumoral lesions of the cervix

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Abstract

Pseudo-tumoral lesions of the cervix implies some reactive, non-neoplastic changes (metaplasia, hyperplasia, inflammation) that, occasionally, are wrong interpreted as precancerous or malign lesions. Even some can present architectural or cytological abnormal aspects, these are different from the one noted in carcinomas or the precursor lesions of carcinomas. Their recognition is indispensable in order to avoid the *diagnose* errors and the super evaluation of these benign lesions.

Keywords: pseudo-tumoral lesions, cervix.

☞ Cervical metaplasia

Cervical metaplasia represents the replace of the endocervical epithelium with tubal, intestinal, squamous, endometrial, transitional or oxyphilic epithelium, proving the multiple potency of differentiation of this paramesonephric channels derivative epithelium.

Squamous metaplasia

The *squamous metaplasia* consists in the replacing of the columnar endocervical epithelium with stratified squamous epithelium developed from the reserve under-columnar cells. The metaplastic squamous cells origin was, for a long period of time, the subject of controversies, but using a reduced group of anti-cytokeratin antibody, the immunohistochemical studies bring proves concerning the provenience of the squamous metaplastic cells from the reserve under-columnar cells. In addition, the vimentine negativity of the metaplastic squamous epithelia excludes them stromal origin [1].

This process is continuous, being more active during fetal development, menarche, pregnancy, later post menopause, inflammatory pathology or oral contraceptives treatment.

Microscopically, the squamous metaplasia goes over some stages. In the initial phases, is noted the hyperplasia of the reserve, under-columnar cells, that are more numerous, the cytoplasm being increasingly eosinophilic since the cell is maturing to squamous cell (Figure 1).

Subsequently, the phase of immature squamous metaplasia, characterized by relative uniform aspect of the metaplastic squamous cells, resembling with the native parabasal cells, with preserved polarity, uniform nuclei and reduced cytoplasm (Figure 2).

Mitosis, always typical, could be present until the

superficial epithelial layers. The cellular maturation occurs to the surface; finally, the mature squamous metaplasia is difficult to differentiate from the native squamous epithelium.

Yet, the metaplastic squamous cells do not contain cytoplasmic glycogen- important criteria of differentiation with the naïve epithelium. Additionally, the metaplastic epithelium could extend to the endocervical glandular structures, with a layer of mucus secreting cells on the surface of the metaplastic area.

Tubal metaplasia

• *Tubal metaplasia* represents the replacing of the endocervical epithelium with cells resembling with the tubal mucosa one. A peculiar aspect is the atypical tubal metaplasia and its association with the *in situ* carcinoma (AIS), when the neoplastic epithelium contains areas of tubal epithelium [2].

Microscopically, in the endocervical lining epithelium, areas of ciliated, clear and intercalary cells, resembling the normal tubal epithelium, are present. Similar aspects could be seeing to one or more glandular clefts in close proximity with the squamous-columnar junction. Tubal atypical metaplasia is characterized by glands lined by ciliated or non-ciliated cells, with big nuclei and multilayered disposed.

Immunohistochemically the HMFG1 and CEA reactions are negative [3].

The differential diagnosis is necessary when the metaplastic gland are profound situated, have irregular shape and dimensions, present nuclear atypia and are associated with hyper-cellularity, or stromal edema. All these aspects could create *diagnose* confusions with AIS or invasive carcinoma.

Yet, absence of the architectural anomalies and a non-significant mitotic activity directs the diagnosis to a benign lesion. If these criteria are insufficient, immuno-

histochemical detection of Ki67 or MIB1 could help the diagnosis.

- *Tubal endometrial metaplasia* of the cervix is characterized by the presence in the endocervix of epithelia resembling tubal and endometrial one. Lesion was observed to patients with conisation, being interpreted as an aberrant differentiation after cervical trauma [4].

Microscopically, the change is similar with tubal metaplasia developed in the endometrium of the estrogenic stimulated woman. Endocervical glands got irregular aspect, or present intraluminal cellular stratification. They look limited by columnar epithelia, sometimes having high nuclear-cytoplasmic ratio, the cells presenting many ciliated or apex secretor aspects, but the endometrial type stroma is always absent (Figure 3).

Differential diagnose of this lesion is made with AIS or cervical endometriosis. Tubal endometrial metaplasia is localized in the upper area of the cervical channel and in the profound area of glandular crypts, AIS affecting especially squamous-columnar junction and the superficial zone of glands.

Additionally, intercalary, serous and ciliated cells and rare or absent, mitosis are noted in tubal-endometrial metaplasia.

For real help are immuno-histochemical reactions for Ki67 and MIB 1, which are nuclear proliferative indicators.

Contrasting with cervical endometriosis, in tubal endometrial metaplasia stroma is fibromatous or leiomyofibromatous.

Intestinal metaplasia

Intestinal metaplasia consists in the presence of intestinal type epithelial cells in the endocervical epithelium. Such changes can appear in atypical hyperplasias of the cervix in association with AIS or invasive carcinoma [5].

Microscopically, between columnar endocervical cells are present goblet and even Paneth cells. In extended metaplasia can occur stromal mucous extravasation, which, because the stromal reactive changes, can determine diagnosis difficulties.

Transitional metaplasia

Transitional metaplasia is developed at elder woman in exocervix. Vast studies concerning the lesion emphasize the medium age of 60, respectively 67.8 year [6, 7].

The term transitional metaplasia is considered incorrect, in fact the change being a basal cell hyperplasia. Was suggesting that lesion could be a variant of exocervical squamous atrophy [7].

Microscopically, an epithelium similar with the transitional one, composed by cells similar with parabasal and basal cells, is present in all the thickness of the exocervical mucosa [7, 8].

Metaplastic epithelium is tall, composed from 10 layers, the cells having the long axis perpendicularly on the mucosa's surface, nuclei being oval or spindle shaped, without cellular atypias.

Exception is made only by the superficial cells, with nuclei orientated parallel with epithelium thickness, similar with normal urothelium.

Immunohistochemically, the cells contain CK20, only limited expressed in the basal cells of the squamous epithelium [9, 10].

Atypical oxyphilic metaplasia

Atypical oxyphilic metaplasia corresponds to the presence of atypical oxyphilic cells in the endocervical epithelium. The lesion was correlated with chronic cervicitis. Jones M. A. (1997) described six cases at patients between 41–62 years, one using oral contraceptive, and one tamoxifen treated for mammary cancer.

Microscopically, endocervical glandular epithelia are replaced by large, cubic or polyedric cells, with dense, eosinophilic, sometimes vacuolated cytoplasm and with different degrees of nuclear atypia. Nuclei are big, hyperchromatic and frequent lobulated or multiple. Despite these aspects, epithelial layering and nuclear atypia are absent.

Histochemically, mucin and glycogen reaction are frequent negative.

Immunohistochemically, reactions for GCDPF 15 and CEA are negative.

Reactive squamous atypia

Reactive squamous atypia is a cervical inflammatory and reparatory related change of the native squamous or metaplastic epithelium.

The etiology of the lesions is not very well established, but to 10–20% of the woman with squamous atypia HPV DNA was detected, considering that the lesion is the most precocious, but unspecific, manifestation of the HPV infection [12].

It is considered that reactive squamous atypia is rather determined by a heterogeneous group of aggressors, most of lesions are not associated with HPV infection.

Microscopically, the lesions consist in a uniform cellular population, with tendency to normal layering and maturation and minimum mitotic activity. The cells have a normal nuclear-cytoplasmic ratio, varied degree of intracellular edema (spongiosis), and the intercellular bridges are usually obvious. Nuclei are oval, with increase of volume, minimum anisocharia and voluminous nucleoli.

Nuclear chromatin is fine granular, nuclear membrane is smooth or slight undulated, occasionally binuclear cells are present. Characteristically, an acute or chronic inflammatory infiltrate is present in stroma and PMN could be seeing in the thickness of epithelium.

Differential diagnose is made with koilocytic atypia and low or high degree CIN.

In epithelium with koilocytic atypia, the general architecture is disorganized and the maturation is abnormal.

Nuclear membrane of koilocytes is unregulated, thickened and a clear perinuclear halo is present.

In low degree CIN, the cells from the inferior third

of the epithelium had large, irregular, hyperchromatic nuclei, with reduced or absent cellular polarity.

In high degree CIN, the proliferation is most intense, the architectural disorganization is important, nuclear atypia severe, with hyperchromasia and intense pleomorphic aspects and atypical mitosis are present.

☞ Epithelioma-like hyperplasia

Epithelioma-like hyperplasia (carcinoma-like) is a reactive lesion of the squamous layered epithelium of the exocervix that usually accompanied inflammatory or tumoral subjacent lesions. These under epithelial lesions act like a chronic irritating factor, causing an exuberant replay reaction of the squamous epithelium.

Microscopically, at the level of the squamous epithelium is noted papillomatosis, acanthosis, parakeratosis and abnormal and unequal elongation of the epithelial crest in chorion. This last change can determine apparition of isolated epithelial islands in stroma subjacent to lesion, which can give the wrong consideration of invasion.

An intact basal membrane delimits the islands; serial sections establish the connection of these islands with the surface of the epithelium. Sometimes could appear unicellular or small group of cells dyskeratosis and the tendency to sketch intraepithelial keratotic pearls, basal membrane is integer, mitotic activity is reduced or absent. In subjacent chorion is an inflammatory infiltrate with PMN (Figure 4).

Differential diagnose is made with microinvasive squamous carcinoma, but the integrity of the basal membrane, the orderly aspect of the basal cells and, generally, the maintenance of the orderly architecture of the squamous epithelium, together with absence of atypical mitosis and invasion of chorion, direct the diagnosis to a benign lesion.

☞ Pagetoid dyskeratosis

Pagetoid dyskeratosis is a reactive process of the squamous epithelia, which can be observed and in exocervix. Between the inductor agents of the lesion, on the first plan are chronic irritants. Val-Bernal J. F. *et al.* (2000) find that 37% of the patients with uterine prolapse and 5% from the one with uterine leiomyoma have this lesion.

Microscopically, a small number of normal keratinocytes proliferate, occurring a premature keratinization, the morphology of the cells becoming reassembling with the one of the epidermal Paget disease.

Immunohistochemically, pagetoid cells are positive for high molecular weight CK and negative for low molecular weight CK, EMA, CEA, HPV.

Differential diagnose is made with glycogen intracellular accumulation and koilocytosis. In the first lesion, squamous cells cytoplasm is clear or vacuolated. In koilocytotic atypia, the general architecture is abnormal.

Koilocytic cells have big nuclei, with irregular, thickened nuclear membrane and a clear perinuclear halo.

☞ Cervical cysts

Cervical cysts are frequent Naboth cysts, rarely being traumatic.

- *Naboth cysts* are cystic dilated endocervical glands, linked to cervical inflammatory processes that determine closing of the glandular ostia, lining epithelia continuing to secrete mucus.

Microscopically, cystic dilatations are lined by mono-layered, mucus secreting, columnar epithelia like the one of the normal or atrophic endocervix, or squamous metaplastic epithelia. Disruption of the cysts and mucin extravasation can determine reactive changes of the cervical stroma and adjacent glands, fact that can create diagnosis difficulties.

Histochemically, lining cells present positive reaction to mucin towards the lumina, element for differentiates from the cystic dilated mesonephric remainder.

Differential diagnose. In the presence of reactive changes of glands and adjacent stroma, differential *diagnose* with invasive adenocarcinoma is necessary. A uniform architectural pattern and the absence of nuclear atypias orientate the diagnosis to a benign lesion.

- *Traumatic cysts* are rare cervical lesions composed by inclusion of the epithelium of the exocervix, frequent related to obstetrical traumas.

Microscopically, cysts are lined by squamous, normal matured epithelia, with basal layer oriented opposite to cavity, and the cystic lumen filled with desquamated epithelial cells.

☞ Glandular hyperplasia

Glandular hyperplasia of the cervix includes simple glandular hyperplasia, diffuse laminar glandular endocervix hyperplasia and microglandular endocervical hyperplasia.

- *Simple glandular hyperplasia (adenoma-like proliferation)* is a common lesion of the cervix with localized proliferation of the glandular clefts. The lesion was described by Fluhmann (1961), which appreciated that its prevalence increases with the age, being present at 8% of the adult women and 13% from the postmenopausal women. Segal G. H. (1990) noted such changes in the cervical channel, more frequent on posterior lip of the cervix and close to squamous-columnar junction.

Microscopically, initial endocervical crypts increase in number, some are cystic dilated and characteristically close together in one or more centers with nodular architecture. Glandular formations are round, have different dimensions, and are lined by mono-layered cubic, squamous metaplastic or endocervical type, columnar epithelium with concentrated mucous content.

They are described two aspects of the lesions: either cystic structures filled with mucin, resembling Naboth cysts, or multiple glands disposed in acini or tubules. Occasionally, aspects of atypia or mitotic activity occur, but both changes are only focal.

Differential diagnose is made with AIS, but simple glandular hyperplasia presents only occasional and focal nuclear atypias or mitotic activity, and glands do not

invades cervical stroma.

- *Endocervical diffuse laminar glandular hyperplasia (unspecific hyperplasia)* corresponds to a distinct variety of glandular hyperplasia circumferential developed in the cervical stroma. As in case of simple glandular hyperplasia, this lesion is an accidental discovery on hysterectomy pieces.

Microscopically they are noted simple hyperplasia of the superficial endocervical glandular crypts, with clear demarcation to subjacent stroma. Hyperplastic glands are placed in uniformly distanced groups. They are lined by mucinous, mono-layered epithelia with increase in volume and have basally placed nuclei. In the specialty papers focal exuberant proliferative lesions with cellular atypia and minimum mitotic activity, but without stromal reaction are communicated [16, 17].

Differential diagnose is made with adenocarcinoma with minimum deviation. In diffuse laminar glandular hyperplasia, profound invasion or irregular infiltrative aspect do not appear and cytologic atypias have only focal character.

- *Endocervical microglandular hyperplasia (EMH)* is a complex proliferation of the endocervical glands epithelia. The lesion is benign, enough commune to women with excessive hormonal stimulation, especially to young patients using oral contraceptives, in estrogenic-progestative treatments, in pregnancy and post partum [18, 19].

The frequency of the lesion on hysterectomy pieces is estimated to 30% of cases [20].

Microscopically, the change is mono or plurifocal. The glands, increased numerically, have reduced dimensions, are “back to back” disposed and are filled with mucin. They are lined by a single layer of cubic or columnar cells, with clear or fine granulated, amphophilic or eosinophilic cytoplasm, having characteristically an under nuclear or/and over nuclear vacuole, containing glycogen. Nuclei are small, uniform and round, with reduced or absent mitotic activity. Sometimes, polymorphism and hyperchromasia can appear, but the mitotic rate remains low, 1 mitoses/field at ob. $\times 10$ [21].

Frequent, in the glandular lumina are present PMN. Associated areas of hyperplasia of the reserve cells and areas of immature squamous metaplasia can be present

The growing patterns of the lesion are: florid, mucinous, solid and with areas of hyalinization. In the florid form, the glands are irregular, with apparently infiltrative aspect; also, they are noted areas with hyperchromasia and pleomorphic nuclei (Figure 5).

Such aspects can be wrong interpreted as adenocarcinoma.

Histochemically, the cells are weak positive in mucin staining, but the intraluminal secretion product is intense positive.

Immunohistochemically, CEA negativity is useful in differentiation between microglandular hyperplasia and cervical adenocarcinoma.

Differential diagnose is made with clear cells carcinoma and cervical adenocarcinoma. Differing from microglandular hyperplasia, clear cells carcinoma have

the tendency to form papillary, glandular-like and tubal structures with invasive growing and presents frequent atypical mitosis. Additionally, cells from the microglandular hyperplasia do not contain glycogen, but cytoplasmatic accumulations of mucin.

Cervical adenocarcinoma can coexist with areas of microglandular hyperplasia, but nuclear atypia, atypical mitosis and stromal invasion solve the diagnosis.

Immunohistochemically, microglandular hyperplasia is in majority of cases CEA negative, and invasive adenocarcinoma is CEA negative occasionally.

☞ Mesonephric rests and mesonephric hyperplasia

- *Mesonephric rests* are vestiges of the mesonephric or wolffian ducts, profound situated in cervix, right to the limits endo–exo cervix. They are present at 15% to 22% of cervixes [22, 23].

Microscopically, mesonephric rests have the aspect of a branching duct, surrounded by small groups of tubular, sometimes cystic dilated glands. Tubular structures are lined by mono layered epithelia, composed by cubic or short columnar unciliated cells. They do not contain either glycogen or mucin, at the same time, tubes lumina can contain eosinophilic, homogeneous secretion product, which contain glycogen or mucin.

- *Mesonephric hyperplasia* is characterized by numerical and sizes increase of the mesonephric tubes, lesions becoming extensively or diffuse florid. Lining cells can present some pleomorphism, together with mitotic activity. Depending on the dominant change, lesion can have some aspects: lobular, diffuse, and intraductal [23].

Rarely, mesonephric hyperplasia can have adenomatous pattern, when occur problems for differentiate from endocervical adenocarcinoma [25]. Exceptionally, literature mentions the mesonephric rests possibility to advance to a mesonephric carcinoma [26].

Differential diagnose is made with AIS. Mesonephric hyperplasia differs from AIS by the absence of complex glandular pattern, mitosis, intracellular mucin and stromal edema. Distinct from the most endocervical adenocarcinomas, in mesonephric hyperplasia CEA is absent and Ki67 is low.

☞ Heterologous tissues

Heterologous tissues, even rare in cervix, can have a variety of histologic aspects. Cartilaginous, osseous, adipose, glial differentiations are mention in the specialty literature. For the reason that these changes are sometimes present in association and occur at woman from the reproductive age, go to the assumption that they are remaining fetal tissues from abortion. Other authors concluded that heterologous tissues belong from a teratoma, or represent a mesodermal metaplasia [27, 28].

Additionally, the presence of differentiations of epidermal annexes, like sebaceous, sweat glands, and hair are mentioned (Figure 6).

These last lesions are named epidermal metaplasia.

Figure 1 – Hyperplasia of the basal layer
(HE staining, ob. ×10)

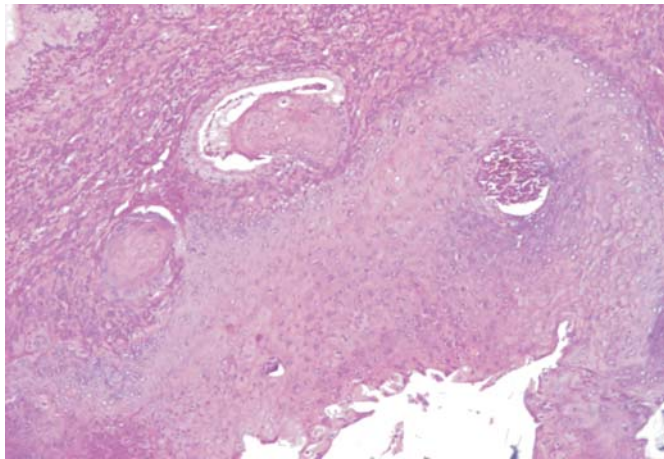
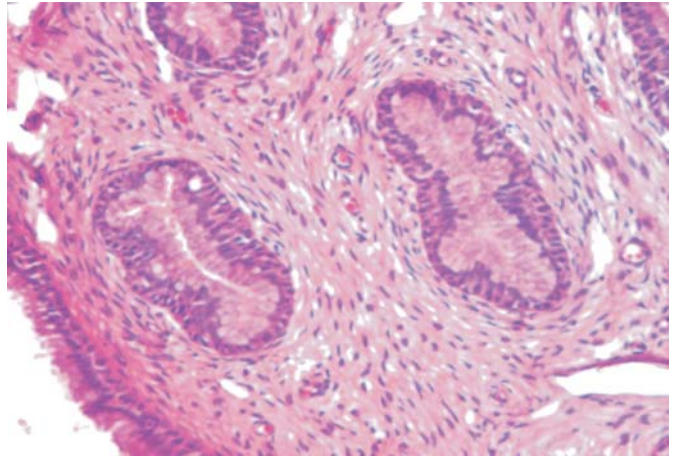


Figure 2 – Immature squamous metaplasia
(HE staining, ob. ×10)

Figure 3 – Tubal-endometrioid metaplasia
(HE staining, ob. ×20)

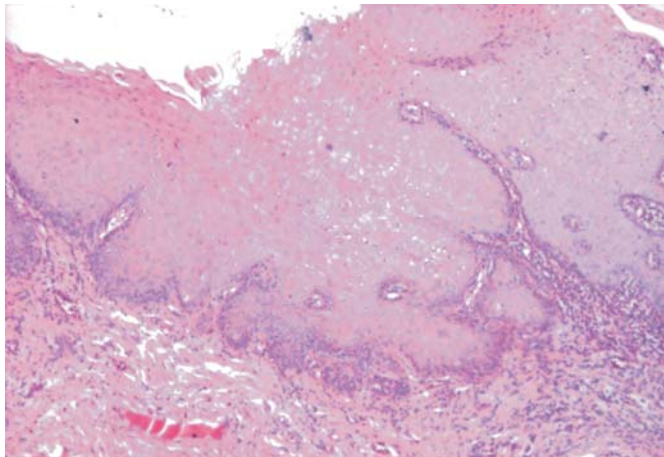
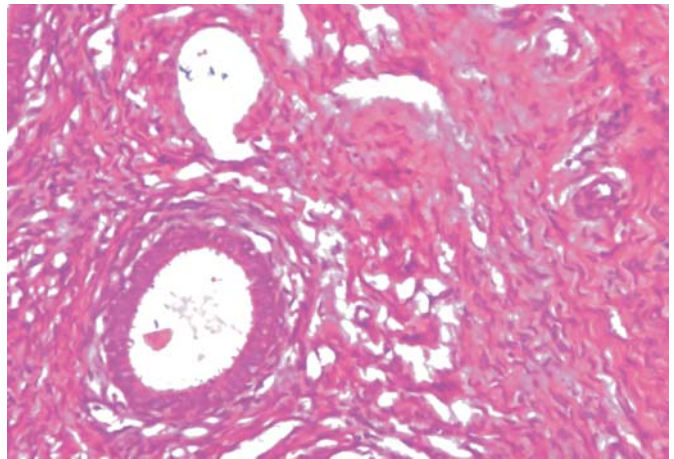


Figure 4 – Pseudo-epitheliomatous hyperplasia
(HE staining, ob. ×10)

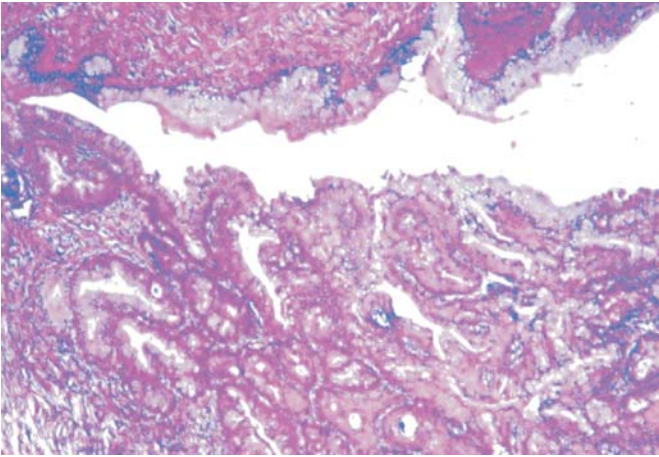


Figure 5 – Microglandular hyperplasia of endocervix, florid form (HE staining, ob. ×10)

Figure 6 – Sebaceous glands differentiation (HE staining, ob. ×20)

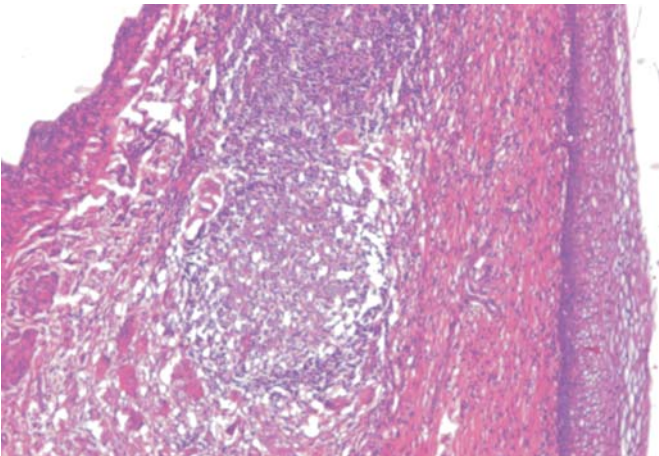
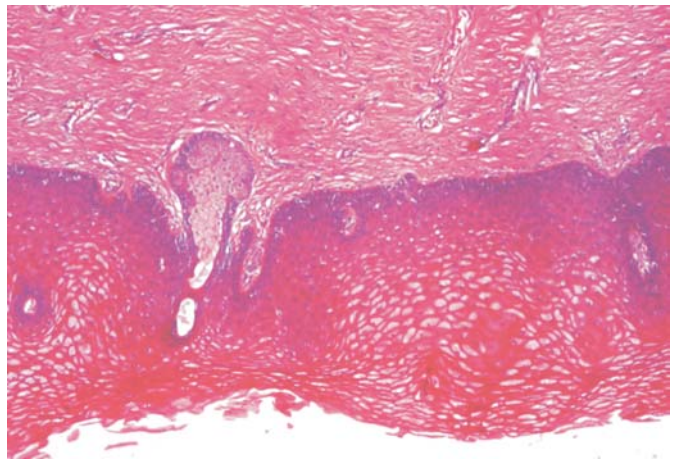
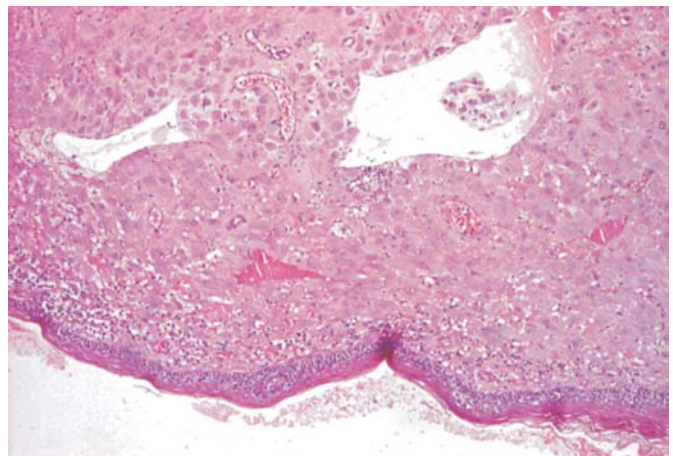


Figure 7 – Cervical pseudo-lymphoma: follicular cervicitis (HE staining, ob. ×10)

Figure 8 – Decidual nodule (HE staining, ob. ×10)



☞ Giant multinucleate stromal cells

Giant multinucleate stromal cells can be noted in the cervical stroma, just under epithelium. Their nature is fibroblastic or myofibroblastic and, associating stromal edema, give sometimes a vague polypoid aspect. Similar changes were described and in other mucosa membrane covered structures, like vulva, vagina, anus, oral and nasal cavity.

☞ Pseudo-neoplastic lesions after cervical surgery

Pseudo neoplastic lesions after cervical surgery are: mesenchymal florid reaction, necrobiosis granuloma, ceroid granuloma and traumatic neuroma.

- *Mesenchymal florid reaction* (after surgery spindle cells nodule) is noted after cervical biopsies, curettages etc. Similar lesions occur and in other structures of genito-urinary tract, especially in vulva and vagina [29].

Microscopically, fibroblastic cells proliferation is uniform and dense, cells being grouped in intersected fascicules or short stripes, separated by edema. Proliferated cells had pale, oval or spindle shaped nuclei, with prominent nucleoli and a generally low mitotic activity, mitosis are always typical.

Characteristically, PMN and red cells presence give to the ensemble of proliferation the aspect of granulation tissue. The change was compared with nodular fasciitis, because the peripheral zones of the lesion can grow infiltrative

Immunohistochemically, lesions are vimentine and desmine positive, with rare cases of low weight CK positivity.

Differential diagnose is made with fibrosarcoma or leiomyosarcoma, which can be excluded by the surgery historic, the absence of nuclear atypias, atypical mitosis and invasion.

- *Necrobiosis granuloma* is a stromal reaction to cervical surgery. Similar lesions were noted in post surgical pathology of prostate, or secondary to diathermocoagulation necrosis, or deposits of metals from instruments, like chrome, nickel, zinc or tungsten [30].

Microscopic the aspect is of foreign body granuloma similar with tuberculosis granuloma or rheumatoid nodule. In the centre is a necrosis area, surrounded by palisade-arranged histiocytes, with scattered giant cells. The lesion evolves to a fibrous scar.

- *Ceroid granuloma (lipofuscine)* is a rare lesion, noted and in other structures of the feminine genital tract. Due to the rarity, the cause and the mechanism of apparition of this lesion is unclear, but was noted its association with areas of endometriosis [31].

Ooi K. *et al.* (1995) consider that the lesion correspond to a lipid substances accumulation in the macrophages cytoplasm, that, in the absence of biologic antioxidant, forms auto oxidants and favor ceroid conversion.

Microscopically, in the superficial stroma, just under epithelia, diffuse or nodular placed macrophagic histiocytes with cytoplasm rich in neuter lipids and ceroid pigment can be observed.

- *Traumatic neuroma* may develop consequently to a complication after surgical treatments on cervix, like conisation.

Microscopically is noted the presence of proliferated nervous fillets, surrounded by a dense fibro-collagen tissue.

Immunohistochemically, the lesion is S-100 protein positive.

☞ Pseudo-lymphomas

Pseudo-lymphomas of the cervix are inflammatory lesions that ask differential diagnosis problems with lymphomas. Young *et al.* (1985) communicated 10 cases and Piura *et al.* found, since 2001, 20 published cases.

Microscopic is noted an abundant polymorphous infiltrate composed by young and mature lymphocytes, plasma cells and PMN. The most frequent the infiltrate is under epithelial is disposed in strip, rarely exceeding 3 mm thickness, the most profound level of the cervical glands. Sometimes, nodular aspects with macrophages, similar with germinal centers, can be noted (Figure 7).

Differential diagnose is made with lymphoma. Pseudo lymphomas are polymorphous lesions with PMN and plasma cells, sometimes making with germinal centers that contain macrophagic type cells. The infiltrates are more superficial located than in lymphomas and the lesions are frequent ulcerated. Finally, immune reactions with monoclonal antibody can solve the diagnosis.

☞ Endometriosis

Endometriosis consists of areas resembling with endometrial tissue. It is a rare lesion, accidental found to patients investigated for other uterine diseases, and can associate similar aspects in myometrium and saplings.

Endometriosis is encounter over 40 years old at multipar woman, with breaks on birth, curettages, cervical biopsies, electro-cauterizations and conisations.

Ismail SM *et al.* (1991) found this lesion on 4% of the cervical biopsy pieces. Some mentioned predisposant factors are dysmenorrhea, precocious menarche, reduced time cycles, all having in common estrogenic level. In the same context, the familial factor was incriminated, being described even a "endometriotic" phenotype [36].

Microscopically, endometriosis consists from typical endometrial glands, frequent resembling with proliferative endometrium, in an endometrial type stroma. Rarely, glands can have a secretory aspect, associating decidualisation if the patient is pregnant or was progesterone treated. Additionally, can be observed macrophages with hemosiderin, lymphocytes, red cells infiltrate or large hemorrhagic areas.

Sometimes the diagnose can be quite difficult. If the stroma can not be seen, diagnose of endometriosis can not be cert and can determine confusions with malign or premalign lesions, endocervical glandular dysplasia and AIS. If glands are absent lesion is named stromal endometriosis, which imposed differential diagnosis with sarcoma [37].

Differential diagnose of cervical endometriosis with endocervical glands hyperplasia and tubal-endometrial metaplasia is based on the aspect of the cells and the absence of endometrial type stroma. In the absence of endometrial stroma, lesion must be differentiated from AIS or glandular dysplasia. In both cases, the absence of glandular atypias orients the diagnosis to endometriosis. Stromal endometriosis, by the absence or the poverty of glands, can simulate a stromal sarcoma or Kaposi sarcoma. The small dimensions of the lesion in endometriosis and the absence of peripheral infiltration plead to the benign lesion.

☐ Pseudo-tumoral cervical lesions encountered in pregnancy

Pseudo-tumoral cervical lesions encountered in pregnancy are: Arias-Stela reaction, decidual nodule and placental nodule.

- *Arias-Stela reaction* can occur in endocervix in the context of a normal or ectopic pregnancy and accompanies molar pregnancy and choriocarcinoma. A study concerning 191 pregnant women found the lesion only in 9% of cases [38].

Microscopically, the endocervical glands changes are similar to the one from endometrium. Endocervical glands are lined by epithelia with hyper secretor aspect, pseudo-layered disposed, sometimes with intraglandular papillary projections. Epithelial cells have large, pleyomorphous, hyperchromatic nuclei that bulge in the glandular lumen, with hobnail aspect, but in most cases mitosis are absent. Cytoplasm is hypersecretant, with numerous vacuoles. Stroma between glands can become decidual, with large, polygonal, eosinophilic cells.

Differential diagnose is made with clear cell carcinoma or AIS. The hypersecretor aspect of the glands, decidual stromal differentiation, and the absence of mitotic activity are arguments for the benign lesion. Additionally, the clinic context of pregnancy solves diagnose.

- *Decidual nodule* is a lesion of some millimeters, placed just under the cervical epithelium. It can be seeing in pregnancy and to the progesterone treated women.

Microscopically is composed from large, polygonal cells, with abundant, eosinophilic, fine granular cytoplasm and normo-chrome nuclei, without mitotic activity. The lesions do not have continuity with the superjacent epithelium (Figure 8).

Differential diagnose with a squamous non-keratinised carcinoma is relative simple, the absence of nuclear atypias and atypical mitosis, orient the diagnosis to the benign lesion. Additionally, immunohistochemical reactions with anti-cytokeratin antibodies are absent in decidual nodule and positive in squamous carcinomas.

- *Placental nodule (trophoblastic)* is just under epithelial situated in exocervix and is composed by an area of trophoblastic cells in involution.

Microscopic the lesion have hyalinized aspect and contains trophoblastic cells, frequent degenerated, with cytoplasmic vacuoles and without nuclear atypias or

significant mitotic activity. It associates chronic inflammatory infiltrates.

Immunohistochemically, the placental nodule cells are CK, human placental lactogen, Mel-CAM positive, and Ki67 low positive [39].

Differential diagnose with unkeratinised squamous carcinoma is made by the absence of nuclear atypias and atypical mitosis in the structure of the placental nodule and the human placental lactogen positivity.

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