The role of cytology in the diagnosis of benign and malignant anal lesions

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Squamous cell carcinoma is a rather infrequent neoplasm of the gastrointestinal tract. Nevertheless its frequency is increasing lately especially in high risk groups of the population infected from HIV or HPV viruses. Squamous cell carcinoma is a slowly and locally growing neoplasm which metastasizes in advanced stages. Its diagnosis must be accomplished by the least traumatic examinations possible. In our study we reviewed our five years experience that included 116 cases. In 89 of them cytological material from ulcerated positions of the anal region was examined. In the rest 27 cytological material was obtained by fine needle aspiration of subcutaneous or submucosal anal lesions. All 116 case reports were retrospectively evaluated. Cytological evaluation revealed 29 cases of normal anal epithelium, 13 granulomas, 12 cases of HPV infection, 28 anal squamous intraepithelial lesions (ASIL), 17 post radiation injuries of the anal mucosa and 17 carcinomas. The neoplasms were further subclassified in 12 well differentiated squamous cell carcinomas, 4 cloacogenic carcinomas and 1 leiomyosarcoma. Histological examination followed the initial cytological diagnosis in 75 cases. The correlation between cytological and histological reports did not reveal any false negative or any false positive result. The agreement between histological and cytological evaluation was absolute. Cytological examination is proved to be an easily accessible and totally reliable, low cost diagnostic method, not requiring any kind of anesthesia. It is well accepted by the patients and of paramount clinical utility for the initial diagnostic assessment, the long term follow up after treatment of anal cancer patients. It is also valuable for the differential diagnosis among benign, premalignant and malignant anal lesions.

Key words: anal intraepithelial neoplasia (AIN), squamous cell carcinoma, cytology, HIV, squamous intraepithelial lesion (ASIL)

INTRODUCTION

Anal squamous cell carcinomas are considered to derive from malignant transformation of already existing intraepithelial lesions.1 Anal intraepithelial neoplasia (AIN) was first described by Fenger and Nielsen, in Denmark after a two-years review of all histological specimens from anal operations.2 They classified AIN by using the Bethesda system, that is the same system universally used for cervical intraepithelial neoplasia classification.

A transitional zone exists in the anal area, where the normal glandular epithelium falls into normal squamous epithelium. The majority of precancerous lesions are first appearing in the transitional zone. AIN is classified histologically into High grade Squamous intraepithelial lesion (HSIL) and Low grade Squamous intraepithelial lesion (LSIL). In the first case (AIN 1), less than 1/3 of the depth of normal epithelium is replaced by atypical basaloïd cells, while in HSIL the two thirds (AIN 2) or the total depth (AIN 3) of the normal epithelium is replaced by atypical basaloïd cells. In AIN 3 lesions one can possibly notice microinvasion of basal cell layer.3

Until recently anal cancer was quite uncommon, appearing to account for 1.5% of the total intestinal neoplasms in the U.S.A.3,4,5 Its frequency is higher in women and in homosexual men.6 Anal cancer’s frequency in the pre-AIDS era, was estimated in 35/100,0007, a frequency almost identical to the one of cervical cancer before the adoption of test Papanicolaou as a periodical screening test. Anal cancer’s frequency is even higher in HIV infected populations.9

Progression of ASIL as well as its possible carcinomatos evolution is correlated with infection of high risk HPV variants, such as no 16, 18, 31, 33, 35, 10,11,12 These genotypes are affecting A6 and A7 regions of human DNA, by inhibiting the well known tumor-suppressing p53 gene and by activating the retinoblastoma transcription factors. The increase of p53 and Ki67 expression
may be proved to be valuable predictors of early intraepithelial neoplasia in the future.

Main risk factors for anal intraepithelial neoplasia are considered to be HPV or HIV infection, CD4 lymphocytes diminution, smoking and anal intercourse. AIN has also been correlated with iatrogenic immunosuppression in patients with transplantation history. AIN is usually asymptomatic. Patients may present pain, itching or hemorrhage. AIN may be multifocal and the patient must be also examined for possible intraepithelial neoplasia of the cervix (CIN), the vagina (VAIN) and the vulvae (VIN).

Anal cancer presents with a large variety of symptoms, many years after AIN. It has a long but possibly fatal clinical course. Many cancerous and precancerous anal lesions present almost identical macroscopic findings and must be included in the differential diagnosis from benign anal lesions. Anal verrucus carcinoma is a well differentiated form of squamous carcinoma. Paget disease is an intraepithelial skin adenocarcinoma with apocrine differentiatation. Basal cell carcinoma, Langerhans histiocytosis and T- skin lymphoma must also be included in the differential diagnosis.

Cytological examination of anal smears ("anal Pap smear") is a widely accepted diagnostic method due to its low economic impact. No previous special preparation of the colon or any kind of anesthesia is needed. Cytological examination allows early diagnosis of precancerous lesions and effective follow up of high risk patients as well as after radio-chemotherapy treatment of anal cancer.

MATERIALS AND METHODS

In our study, we examined cytological material which was collected by brush from ulcerated anal lesions (89 cases) as well as cytological material from fine needle aspiration biopsies of submucosal lesions (27 cases). Cytological results were reviewed and analyzed. 55 patients were men. Patients mean age was between 24 and 64 years old (mean age 40,2 years). 8 patients had a known history of anal intercourse.

Cytological specimens were examined independently by 2 specialized cytopathologists who estimated specimens cellularity, the presence of anucleate squamous cells, transitional zone cells, parakeratotic, dyskeratotic or cancer cells.

Specimens findings were classified according to the internationally accepted Bethesda system in:

- atypical cells of undetermined significance (ASCUS),
- low grade anal squamous intraepithelial lesion (low grade A-SIL)
- high grade anal squamous intraepithelial lesion (high grade A-SIL)
- squamous cell carcinomas
- others neoplasms

Histological examination followed in 75 cases. Its findings were compared to the respective cytological findings.

RESULTS

Cytological examination revealed 29 cases of normal squamous epithelium, 13 granulomas, 12 cases of HPV infection, 28 intraepithelial lesions, 17 post radiation injuries and 17 neoplasms.

Neoplasms were further classified in 12 well differentiated squamous carcinomas, 4 cloacogenic carcinomas and 1 leiomyosarcoma.

Sixteen of the 29 cases with normal cytological findings were histologically examined. Histological examination confirmed the initial cytological diagnosis. Nine of the 13 cases in which cytology revealed the presence of granulomas, were histologically evaluated. Histological examination confirmed the initial cytological diagnosis in all cases. Six of the 12 cases in which cytology revealed HPV infection, were histologically examined after local surgical biopsy. Histological results confirmed the initial cytological diagnosis. Thirteen from the 28 cases in which intraepithelial neoplasia was revealed by cytology, were further examined histologically. Histological evaluation revealed 7 low grade squamous intraepithelial lesions and 6 high grade squamous intraepithelial lesions. All 14 cases in which cytology revealed post radiation injury were histologically examined and followed up cytologically for a long period of time without any false positive or any false negative result. Histological examination of the 17 cases which were cytologically diagnosed as neoplasms revealed 12 well differentiated squamous carcinomas, 4 cloacogenic carcinomas and 1 leiomyosarcoma.

In general, correlation between cytological and histological findings did not reveal any false negative or false positive result and accordance between cytological and histological findings was absolute.

DISCUSSION

Anal smear cytological examination is proved by our study to be a reliable diagnostic method, easily accepted by the patient and clinically valuable as a screening tool for high risk patients, due to its low economic cost.

There are not enough studies in the literature referring to anal cytology. Few existing ones claim that anal cytology presents low specificity and specificity in diagnosing early intraepithelial lesions. The poor results of these studies are probably caused by methodological problems referring to the statistical elaboration of cytological findings. Palefskyestimates the anal cytology sensitivity at 69% in 407 HIV-positive and at 47% in 251 HIV-negative homosexual or amphisexual men. Palefsky is also reporting that histological findings do not always correspond to the cytological ones in cases of anal intraepithelial neoplasia. In our study we did not observe any discordance between cytological and histological results. The use of Thin prep technique is referred by an other study, as a method with very promising results, presenting sensitivity of 92% in diagnosing precancerous and neoplastic anal lesions. Panther reports that anal cytology presents only 47% sensitivity in detecting precancer-
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Benign and neoplastic lesions. This poor outcome in Panther study may have been caused by methodological problems. Anal intraepithelial neoplasia is a possibly precancerous condition whose early detection and management is difficult but crucial for the patient’s final outcome. Although the use of highly active antiretroviral therapy (HAART) has reduced the number of opportunistic viral infections, AIN is nowadays diagnosed more often than in the past.

Anal cancer occurs more often in homosexual men, while anal intraepithelial neoplasia is encountered as frequently as cervical intraepithelial neoplasia before the wide use of Papanicolaou test in the everyday clinical practice. Epidemiological studies reveal that anal and cervical intraepithelial neoplasias present similar biological behaviour and etiological correlation with HPV infection.

Periodical cytological examination of anal smears of high risk patients can be a valuable diagnostic test for the early detection of possibly precancerous anal lesions.

A crucial question refers to the possibility of progression of AIN to squamous cell carcinoma. Although epidemiological data remains poor and contradictory, it is estimated that about 1% of AIN is progressing to invasion of AIN to squamous cell carcinoma. Although high risk patients can be a valuable diagnostic test for the behaviour and etiological correlation with HPV infection.

The majority of AIN do not progress to squamous cell carcinomas. All abnormal cytological examinations should be followed by endoscopic examination of the anal canal and the rectum and probably histologic examination of any endoscopically located lesion under general anaesthesia. In case of cytologically diagnosed AIN 1 and AIN 2, anal pap smear must be repeated every 6 months for 3 consecutive times. If no pathological findings are revealed in the next pap smears, cytological examination can be repeated once a year. In case of cytologically diagnosed AIN 3, surgical excision of the suspicious lesion is advised while anal pap smear must be repeated periodical for 5 consecutive years. A multifocal or large AIN 3 lesion may require wide excision. Anoscopy and cytological examination must be repeated every 6 months after the surgical excision in order to detect as early as possible any local relapse, whose frequency is estimated around 30% for the first 5 years after surgical excision.

Usually AIN can be treated conservatively. In a recent study, it was estimated that 74% of all AIN 3 cases were treated conservatively, without any surgical intervention. Usually, multifocal or large AIN 3 lesions require surgical excision. In a recent study of 11 patients with AÆI 3 lesions that were surgically excised, only 4 of them relapsed in a 34 months period after surgery. The high relapse rate for AIDS patients presenting AIN 3 lesions indicates that a long term follow-up of these patients is indispensable.

Preventive cytological programs for high risk populations have been tested with great success, presenting high sensitivity and specificity as well as low economic cost. Combination of cytological examination with anoscopy and histological examination increases even more the method’s sensitivity and specificity. Recent studies about the cost effectiveness of preventive anal cytological examination of high risk patients, have revealed that periodical anal pap smear (every year for HPV positive and every 2-3 years for HPV negative populations) can reduce considerably the frequency of anal intraepithelial lesions and anal cancer.

Future developments about early detection and treatment of AIN include the application of a widely accepted preventive diagnostic protocol, the better information of clinicians about the importance of AIN early diagnosis, as well as the application of new therapies, combining surgical excision with immunotherapy, chemotherapy and radiotherapy.

SUMMARY

ULOGA CITOLOGIJE U DIJAGNOSTICI BENIGNIH I MALIGNIH LEZIJA


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