COEXISTING CERVICAL NON-KERATINIZED SQUAMOS CARCINOMA AND TUBERCULOSIS. CASE REPORT. LITERATURE REVIEW

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Abstract

A 29 yrs Caucasian woman, sequelar of lung tuberculosis with cervical squamous non-keratinised cancer stage IB, diagnosed by multiple cervical biopsies, has suffered radio-chemotherapy, and a Wertheim's radical hysterectomy with bilateral pelvic node excision, with normal evolution.

The pathological examination of postoperative uterus revealed endocervical tuberculosis associated to exocervical persistent small island of cancer. There are revisited published cases with the coexisting pathologies since their first registration, the reported case being the second in Romania after 50 years, and the knowledge, controversies, hypothesis on the pathogenesis of life-threatening coexistence of high risk oncogenic HPV- genotype 33 in the reported case, and Mycobacterium tuberculosis (BK), and explanations about specific defense, and stimulatory/inhibitory effects of infectious factors, direct/indirect mechanisms. Endocervical tuberculosis is secondary to lungs pathology, HPV reduces cervical relative immunity to BK, and may contribute to loss/ somatically-acquired mutations of a major tumor supressor LKB1, similar to p53, positive in this case. BK reduces immunity to high risk HPV, and the authors speculate that BK is associated to loss/mutations in LKB1 tumor suppressor, because cancer persistency after radio-chemotherapy.

Rezumat: Coexistenţa carcinomului de col scuamos nekeratinizant şi a tuberculozei. Prezentare de caz şi review al literaturii.

Se prezintă şi discută cazul unei femei de 29 ani, cu sechele de tuberculoză pulmonară, diagnosticată prin biopsii cervicale multiple cu carcinom scuamos nekeratinizat cervical stadiul IB, şi care după radiochimioterapie suferă limfadeno- colpo- histerectomie totală cu anexectomie bilaterală cu evoluţie normală.

Examenul histopatologic postoperator relevă tuberculoză endocervicală asociată cu mici insule persistente de carcinom exocervical. Se revăd cazurile publicate cu această rară asociere patologică de la prima înregistrare, cazul raportat fiind al doilea din România după 50 ani, ca şi cunoştinţele, controversele, ipotezele asupra coexistenţei HPV înalt oncogen - genotip 33 în cazul prezentat, şi a Mycobacterium tuberculosis (BK), a mecanismelor defensive directe/indirecte, a efectelor inhibitorii/stimulatorii ale factorilor infecţioşi. Tuberculoza endocervicală este secundară celei pulmonare, HPV reduce relativa imunitate cervicală la BK, şi poate contribui la pierderea/ apariţia mutaţiilor somatice a supresorului tumoral major LKB1, similar p53, pozitiv in acest caz. BK reduce imunitatea la HPV cu risc, autorii speculând că BK se asociază cu pierderea/apariţia mutaţiilor somatice a supresorului tumoral major LKB1, datorită persistenţei insulelor de cancer după radio-chimioterapie.

Cuvinte cheie: carcinom, tuberculoză, col uterin

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KEY WORDS: carcinoma, tuberculosis, uterine cervix

Introduction

The coexisting cervical pathologies of carcinoma and tuberculosis are rarely reported in the last 20 years, and only in countries from Africa, and Asia - China and India, the host's answer to infectious factors being incomplete known, and controversial. *Mycobacterium tuberculosis* (*BK*) and *high risk oncogenic HPV* have stimulatoryl/inhibitory effects on infected cervical cells, by direct, and indirect mechanisms.

Case report

A Romanian Caucasian woman, 29-years-old, merchandise, low income, married, with a single sexual partner, G3P2, considered healed from pulmonary tuberculosis (2002), but sequelar, is diagnosed with non-keratinizing squamos carcinoma stage IB, *HPV* - genotype 33, p53 positive, with pre-surgery radio-chemotherapy, and Wertheim's radical hysterectomy with bilateral pelvic lymphnodes excision, *per primam* healed, and normal post-surgery evolution, without pulmonary tuberculosis reactivation (2008).

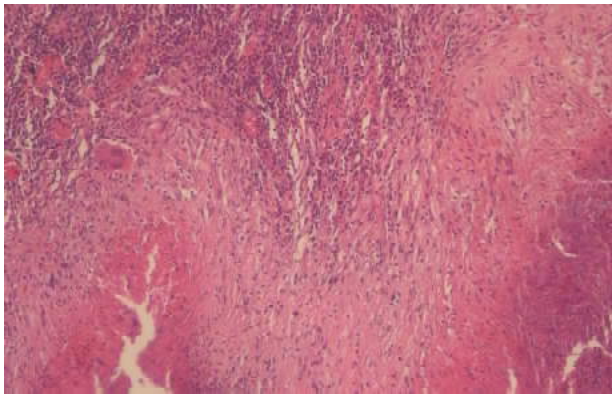
The post-surgery pathological examination showed a cervix with large areas of ulceration, polymorph inflammatory infiltrate, and foreign body multinuclear giant cells, micro-calcifications, small islands of squamos non-keratinizing cancer cells. The endocervix presents a granulomatous inflammation with Langhans multinuclear giant cells, and with caseous necrosis. The vaginal part, and the lateral part of the cervix have no carcinoma invasion. The endometrium is atrophic, the ovaries have *albicans* bodies, the tubes have hypoplasic mucosis, and the examination of 10 lymphnodes shows reactive aspect, lipo- dystrophy, and micro-calcifications.

Because rarity of the pathological association- uterine cervix carcinoma and tuberculosis, the slides were analyzed by a second pathologist from the highest level of Romanian Pathology, who confirmed the diagnosis.

Literature review

In the 19th century there was a controversy as to whether tuberculosis and cancer can coexist in the same organ; Carl von Rokitansky (1855) was the first to propound the view that there is a definite antagonism between the two, meaning that tuberculosis, and cancer cannot be present in the same organ, but after the influence of work of Votta J Paul, and through his own further experience, Rokitansky later changed his previous generally accepted view and admitted that tuberculosis and carcinoma can coexist, but that this coexistence is rather rare. The case is presented for its rarity in Europe, and to the best of authors' knowledge, after the description in the 19th century last years in Europe (von Franke, 1894- 3 cases, von Recklinghausen,

A



B

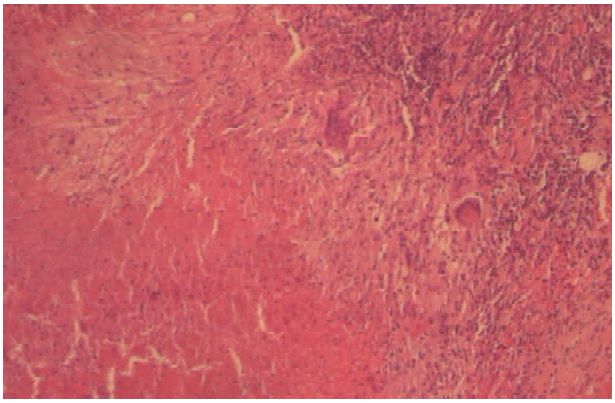


Figure 1

A: epithelioid granuloma with central necrosis (caseous granuloma) with Langhans-type giant cells (with many nuclei arranged in a horseshoe-like pattern at the edge of the cell) around the periphery of the granuloma, and a rich lymphocytic inflammatory infiltrate. HE stain 10x

B: two confluent epithelioid caseous granulomas with Langhans-type giant cells and lymphocytic inflammatory infiltrate at the periphery. HE stain, 10x

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1886; Ross- 1899) there was a small number of reported cases in other non- European world areas, by David M, Scharpman 1940; Yamabe T, Nakayama M, Suzuki K,1972 – Japan [1]; as the citations of Hsu C, Lin YN, et al (1985) [2]. The Chinese authors had analyzed the history of the coexisting cervical pathologies from Europe, China, Japan as it was previously mentioned. In United Kingdom it is described the association of cervical tuberculosis with other viral infection- HIV [3].

In Europe in the last 50 years there are described two similar cases in Romania (Iaşi) [4], and one case in Poland, which is similar to the reported one, uterine cervix tuberculosis after radiation therapy for cervical cancer [5]. Romania is an European developing country, where cervical cancer is a major medical, and socioeconomic burden since the last 25 years, and tuberculosis is becoming other such a burden, as in many other worldwide areas.

In the last 30 years, these coexisting pathologies are reported in developing countries from Asia, as China [2], and India [6]. In a recent report from an oncology center in India, over a 15-years period, tuberculosis in association with malignancy was studied [7]. Highest incidence occurred in head and neck cancer (42%) followed by gastrointestinal cancer (14.1%), lung cancer (13.8%), hematological cancer (10.7%), reproductive cancer (10.3%) and miscellaneous group (9%).

Besides rarity, other discussion in the literature is that tuberculosis may simulate cervical cancer in peri-, and postmenopause [8; 9; 10; 11], because the symptoms of irregular bleeding, postcoital bleeding, with different cervical clinical findings - exophytic with papillary or vegetative growths, tumoral- granulomatous, ulcerative, milliary appearance, and polypoid endocervical aspect [12; 13; 14; 15; 16; 17; 18], being also discussed the possibility of being completely asymptomatic [11].

Many studies have suggested mechanisms for the initial events in the lung tuberculosis, but most were based on experiments carried out *in vitro* with cell lines. Such conditions do not provide information about the real sequence of events taking place when the bacilli gain access to the lung or other organs. There are more studies regarding lung tuberculosis, and it is still not known why some individuals develop the disease whereas the disease remains latent in others, and none of the best research laboratories worldwide have elaborated an appropriate tuberculosis model for its investigation. It is known that in the infected organ the neutrophils are first line of defence against tuberculosis, being activated by *Mycobacterium tuberculosis* products, like the macrophages, but after granuloma formation they have no role, different from macrophages, and the neutrophils return to the infection site only when the granuloma starts to become necrotic (bacterial dissemination). Neutrophils and macrophages release various cytokines to recruit different populations of cells, including more macrophages, to the infection site [19], organizing the granulomas. This structure is developed by the host to contain the infection, and to eliminate the bacteria, but the bacteria persist in a latent state within the granuloma, often for decades. The caseous necrosis from granulomas' center represents an area where on discover the presence of the *Mycobacterium tuberculosis*, which first induced the stimulation of macrophages, and afterwards have destroyed the structural cells of the host, the defence innate and acquired immune cells, and where the bacteria may stay long time in a latent state. The bacilli subsequently reactivate in 10% of the latently infected individuals. The granuloma provides the Mycobacterium tuberculosis and non-tuberculosis with a niche in which it can survive, modulating the immune response to ensure its survival without damage over long periods of time We cannot accurate appreciate if endocervical tuberculosis of the reported case is from the moment of lung tuberculosis diagnosis, since 2002 or after cervical HPV acquisition, or after chemo and radiotherapy.

There are different opinions in the history of cervical tuberculosis diagnosis, and there were proposed many procedures. Since long time [20] it is proposed cytological examination- the Pap smear showing no dysplasia, special staining for acid-fast bacilli, cultures on the Lövenstein medium, PCR for *Mycobacterium tuberculosis*, and indirectly the histopathological examination of endocervical curettage, and of cervical biopsy. .

The cytologic examination is revealing the presence of epithelioid, and multinucleated histiocytic cells of Langhans type [21; 22; 23]. Epithelioid cells are elongated cells with pale eosinophilic cytoplasm, indistinct cell borders, and large elongated/oval nuclei with a delicate chromatin pattern in singles/clusters. Multinucleated histiocytic cells, typical of Langhans cells type, have large number of delicate, ovoid nuclei, some overlapping, arranged peripherally and often in horseshoe shape. The bacteriology with positivity for tubercle bacillus, with the consideration that isolation of the *Mycobacterium tuberculosis* is the gold standard [3]. In one study, staining for acid fast bacilli was not found to be very useful in making the diagnosis [24].

Molecular probes for *Mycobacterium tuberculosis* may be more sensitive than culture, are lower time consuming to obtain the results, but have also reduced specificity [3].

The histological examination of a cervical punch biopsy specimen. may show granulomatous inflammation with caseous necrosis. It is also possible that up to one-third of the cases to have negative culture [3]. The diagnosis of tuberculosis in the Romanian case is sustained by the Langhans multinuclear giant cells discovery, - which make the diagnosis of a granuloma, and the caseous necrosis presence in the central area of the granuloma shows the specific tuberculoid type of the granuloma. Culture for *Mycobacterium tuberculosis* was not possible, as the granulomas were noted on the formalin fixed paraffin embedded cervical tissue, after chemo-and radiotherapy, and post-surgery. In authors' opinion the presence of caseous necrosis in the endocervical stroma is sufficient for the positive diagnosis of cervical tuberculosis, as it is appreciated by other pathologists [25], but many researchers consider that it is very important to distinguish between the granulomatous reaction, and tuberculosis by more specific methods [26]. We can make a discussion about the changes induced by radiation-therapy in the distribution of the nuclei, and the confusion to multinucleated histiocytic giant cells.

There are discussions on other causes of granulomatous cervicitis, as schistosomiasis, amoebic infections, tularemia, brucellosis- specially for patients from Asia, and Africa, sarcoidosis or a foreign body reaction to suture, cotton, cristals [3]. In the last 30 years on assists to an increase of tuberculosis' incidence in conjunction to the HIV pandemic [3]. Tuberculosis (TB) of the uterine cervix was first described by Renaud in 1831, as an uncommon finding, being extremely rare without other genital involvements. In developing countries like India, TB is a major socioeconomic burden, afflicting 14 million people mostly in the reproductive age group (15- 45 years). Fallopian tubes are involved in almost all the cases of pelvic tuberculosis, endometrium in 50 to 60%, and ovaries in 20 to 30% [6]. Cervical tuberculosis accounts for 0.1- 0.65% of all cases of the disease, and 5- 24% of genital tract [27], and is uncommon in developed world [3]. In this case, the presence of the viral infection is clearly proved. The endocervical curettage which could diagnose the associated endocervical tuberculosis was not done, because authors' believe that exocervical malignant lesion was the only cause of the abnormal bleeding. Tuberculosis is usually secondary to a primary focus elsewhere in the body, most commonly the lungs, pleura, mediastinum, lymph-nodes. The spread to the uterine cervix is either by hematogenous, lymphatic dissemination from the infected tube, or by direct extension from the endometrium. There is a relative immunity of the cervix to tubercular infection probably because the Koch bacillus is not able to penetrate the squamous epithelium *of portio* vaginalis, the cervical mucus exerting resistance, but in rare cases, cervical TB may be a primary infection, *Mycobacterium tuberculosis* may be introduced by a partner with tuberculous epididymitis or other genitourinary disease [28]- the reported patient's sexual partner was negative for pulmonary TB.

The question is whether tuberculosis is previous to cancer, or the presence of the viral infection made possible the secondary location of the *Mycobacterium tuberculosis.*

The pathological examination did not revealed extensive granulomatous reaction, or cancer metastases in the endometrium, tubes, ovaries, and lymph nodes.

Since are many years from the first description of this association of these life-threatening

pathologies, host response as the basic mechanism of specific defense against infection and tumor factors that enable such a response are not completely known [29], both of them can benefit from the host's previously compromised immunity: the tubercle bacilli and the virus can potentate each other. The BK is a facultative intracellular parasite that grows well in non-activated macrophages. The intra- and extra-cellular *M. tuberculosis* from the macrophages are destroyed by *granulisin* and *perforin*, detected in the lymphocytes T Vγ9/Vδ2, thus protecting the host from tubercule bacilli [30], and this is a part of the explanation of latent progression of the disease, in people infected with *M. tuberculosis* appearing healthy, and the interplay between the pathogen and the localized tissue response is critical to understanding the progression of infection to active disease.

The γ/δ T cells are nonconventional T cells, and are considered to act as an intermediary between the innate and adaptive immune responses. When large numbers of these bacilli have grown intracellular within such macrophages, a cytotoxic immune response, herein called tissue-damaging delayed-type hypersensitivity kills the macrophages, forming the caseous center of the granulomatous tubercle, where the *M. tuberculosis* is surviving; such a delayed-type hypersensitivity was first described for the pulmonary tuberculosis [31], and more than this, the observation that the bacilli are growing inside macrophages at the cavity surface of the lung tuberculosis is contrary to common dogma, which presumes that bacillary replication at this site is extracellular, and the reported case have suffered of pulmonary tuberculosis **7** years previously.

The progression of cervical dysplasias to invasive, lethal cervical cancers has been attributed to diverse factors such as immune, hormonal, and nutritional status, or co-infection with other sexually-transmitted agents, supporting data being equivocal [32]. Insertional mutagenesis by HPV is another proposed tumor-promoting mechanism, but recent studies have not supported this hypothesis [33]. No common, recurring genetic alterations that cooperate with HPV to promote cervical cancer progression have been identified since Harald Zur Hausen [34] first identified HPV as the causal transmissible agent of cervical cancer near fourty years ago (1976). TB may provide an immunological profile that is associated with an increased susceptibility to HPV, to permit HPV persistency, and nuclear cervical cells' atypia [35] effects which are similar to that of herpes zoster, or candidiasis [36].

The tuberculous granuloma, where ever is located is a hallmark of the unsuccessful host defence mechanisms providing a safety shelter for the bacteria; the distinct cellular response is considered a histologic hallmark for a protective immune response, involving both innate and adaptive immunity. On the other face of the mechanisms against infection, on cannot forget the role of the associated inflammation, because the same cells, molecules involved in the antimicrobial protection are working in the deleterious effects of inflammation [37]. To the pressing question to the biological basis of cervical cancer progression which is to be resolved since long time, is the discover of the loss of a major tumor supressor *LkB1* [38; 39], or somatically-acquired mutations of this tumour supressor *LKB1* [40], which is considered to be similar to p53. It was demonstrated the presence of somatic mutations and deletions of *LKB1* in adenocarcinoma, squamous cell carcinoma, and adenosquamous carcinoma [40], and it was proved that these mutations/deletions are occuring *in vivo*, not after fixation, and this fact is driving the disease progression.

The tumour supressor *LKB1* is working by arrest the cells growth in the phase G1 [41], and by supressing the invasion and metastases, or with other words the mutations in genes of *LKB1* are inducing the conversion of *in situ* dysplasias to invasive carcinomas, and their progression, events first discovered in connection to Peutz- Jeghers Syndrome [42], and pulmonary cancer [43]. When *LKB1* deficiency/mutations are present, a primary cervical tumor confined to the cervix at the time of diagnosis has a bad prognosis: early metastasis and patient death, after the initial diagnosis despite aggressive therapy including radiation treatment [40]. It is known since long time [44] that the diagnosis and treatment of tuberculosis in a patient with cancer assumes a high morbidity and mortality [45]. The

Mycobacterium tuberculosis was proved to reduce host's immunity to high risk HPV types for cervical cancer. It was demonstrated [34] an increasing magnitude of effect of tuberculosis with increasing severity of cervical intraepithelial neoplasia in an isolated women population from rural China- Shanxi Province, as is demonstrated by the increasing odds ratios from 1.68 for HPV positivity, to 1.75 for persistent HPV and then 2.08 for CIN3+.

We speculate that *Mycobacterium tuberculosis* is associated to the loss/mutations in *LKB1* tumor suppressor, because persistency of small islands of squamuos non-keratinizing cancer cells in the cervical specimen obtained post-surgery after aggressive therapy- pre operative radiation- and chemo- therapy, and p53 presence. The same effect of loss/mutations in *LKB1* was supposed to be and analyzed in cases with lung cancer [42]. Besides these, a more virulent *Mycobacterium tuberculosis* induces plasma membrane disruption, inhibits membrane repair, and apoptosis to avoid innate host defense by driving the infected macrophage into necrosis. Necrosis is a mechanism used by bacteria to exit macrophage, evade the host defenses, and disseminate while apoptosis is associated with diminished pathogen viability. [46, 47], and apoptosis is an innate defense function of macrophages against *Mycobacterium tuberculosis* [48] which is in contrast to attenuated *Mycobacterium tuberculosis* causing apoptosis, which limits bacterial replication and promotes T cell cross-priming by antigen-presenting cells

Conclusion

Coexisting cervical pathologies as carcinoma and tuberculosis described since more than 100 years are a challenge for actual medical staff, for understanding modern cellular biology, regarding early diagnosis, and adequate therapy to reduce the high life threatening risks worldwide.

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