

THYROID CARCINOMA IN CHILDREN AND ADOLESCENTS RESULTING FROM THE CHERNOBYL ACCIDENT: POSSIBLE CAUSES OF THE INCIDENCE INCREASE OVERESTIMATION

Jargin S.V.

Peoples' Friendship University of Russia (Moscow)

Souhrn

Vzestup incidence tyreoidálního karcinomu dětí a dospívajících v důsledku havárie v jaderné elektrárně Černobyl: možné příčiny nadhodnocení

Významné zvýšení incidence karcinomů štítné žlázy dětí a dospívajících v důsledku havárie v jaderné elektrárně Černobyl je považováno za prokázané. Data o dramatickém vzestupu s počátkem v roce 1990 jsou však pro patology obeznámené s dobovou diagnostickou praxí zpochybnitelná. Riziková populace byla po havárii podrobena lékařskému vyšetřování a ultrazvukovému screeningu štítné žlázy. Vysoká onkologická ostražitost mohla spolu s omezenými technickými možnostmi a zastaralým vybavením histologických laboratorí přispět k falešně pozitivním závěrům. Diagnostická punkce štítné žlázy tenkou jehlou je doprovázena relativně vysokým podílem nejistých závěrů, kde je indikována histologická verifikace. Ke zhodnocení nukleárních kritérií papilárního tyreoidálního karcinomu (matnicová jádra, intranukleární inkluze atd.) je nezbytná vysoká kvalita histologických řezů. Posouzení kritérií malignity folikulárního tyreoidálního karcinomu jako jsou kapsulární a vaskulární invaze také vyžaduje četné kvalitní řezy. Odpovídajícího počtu a kvality histologických řezů tehdy často nebylo dosahováno, zejména bylo-li použito zalévání do celoidinu. K nárůstu incidence mohly přispět rovněž latentní karcinomy a vysoce diferencované nádory s nejistým maligním potenciálem odhalené při screeningu.

Klíčová slova: tyreoidální karcinom – nádory dětského věku – černobylská havárie – radiační patologie

Summary

Thyroid Carcinoma in Children and Adolescents Resulting from the Chernobyl Accident: Possible Causes of the Incidence Increase Overestimation

The Chernobyl accident in the nuclear power plant on 26th April 1986 was followed by numerous publications overestimating the medical consequences of the disaster. In the publications, interpretations of spontaneous diseases as radiation-induced, indication of radioactivity or dose levels without confrontation with the natural radiation background, or conclusions about incidence increase without comparison with the increase tendencies in larger regions or the whole country, can be found. Improved diagnostics after the Chernobyl accident is not always taken into account. The high figures could have been caused in some cases by non-random material selection or inadequate morphological assessment of biopsy specimens. The application of the linear-no-threshold theory to the inhabitants of contaminated areas contributed to an overestimation of medical consequences of the Chernobyl accident as well. The incidence increase of thyroid carcinoma in children and adolescents started in 1990, four years after the accident. High tumor expectancy after the accident, in the circumstances of limited technical possibilities and outdated equipment of histological laboratories, contributed to a higher number of registered cases. The quality of specimens necessary for the assessment of nuclear criteria of papillary carcinoma was not always achieved at that time. The incidence increase of thyroid carcinoma can, at least in part, be explained by improved detection of thyroid nodules with occasional false-positive conclusions about malignancy. Besides, latent carcinomas and well-differentiated thyroid tumors of uncertain malignant potential, diagnosed as malignancies, could have additionally contributed to the high figures.

Key words: thyroid carcinoma – pediatric cancer – Chernobyl accident – radiation pathology

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Thyroid carcinoma (TC) in children and adolescents is the only type of malignancy, significant increase of which in consequence of Chernobyl accident (CA) is regarded to be proven (3,7,21,29). Reaction of scientific community to the reports on its drastic increase, started 4 years after the CA, was skeptical: it had been assumed that radiation from ^{131}I is less carcinogenic to the thyroid than external radiation, and that a latent period for thyroid carcinoma after an exposure should be around 10 years. There was also uncertainty about accuracy of the diagnoses (30). High incidence and the short induction period were designated as unusual in the UNSCEAR 2000 report, where it is also stated that the number of thyroid cancers in children and adolescents exposed to radiation is considerably higher than expected on the basis of previous knowledge. It is assumed that other factors may be influencing

the risk (29). Improved diagnostics, registration and reporting were named among factors that could have contributed to the increased cancer incidence after the CA (7). It is also noteworthy that exposures to ^{131}I from medical procedures have not demonstrated convincing evidence of an increased thyroid cancer risk (13).

Previously, we reviewed several publications overestimating radiation-induced abnormalities after CA (14–17). This article is based on experience of histopathological practice in the former Soviet Union (22) visiting cytological and histopathological laboratories, and interviewing physicians in the northern regions of Ukraine. Besides, information from Russian-language professional literature can shed more light on the issue. All quotations below are verbatim translations.

The following figures can give an estimate of the incidence

increase. In Ukraine before CA, about 12 cases of TC were registered in children and adolescents yearly. During 5 years preceding the CA (1981-85), a total of 59 cases of thyroid carcinoma were diagnosed among patients younger than 18 years. By the year 1997, the total number of thyroid carcinoma cases, registered in Ukraine in children and adolescents, was 577 (27). In Belarus, TC incidence in some areas increased after the CA from 0,04 to 20-50 cases pro 100.000 children (11). From 1992 to 2002 in Belarus, Russia and Ukraine more than 4000 cases of thyroid cancer were diagnosed among persons who had been children and adolescents at the time of the accident (8).

At the same time, it is known that coverage by medical examinations of the population at risk after the CA was significantly improved. Ultrasonic thyroid screening was performed and large number of thyroid nodules found. Equipment of histopathological laboratories was poor and outdated; excessive thickness of histological sections hindered reliable assessment of diagnostic criteria. Gross dissection of surgical specimens was often made with blunt autopsy knives, without rinsing instruments and cutting board with water, which can result in tissue deformation, contamination of the cut surface by cells and tissue fragments and other artifacts, hardly distinguishable from malignancy criteria. It could have contributed to unusually high frequency of tumor cell finding in blood vessel lumina (45 %) reported in post-Chernobyl pediatric TC (11). In many laboratories celloidin embedding was used, not allowing reliable evaluation of nuclear changes in papillary thyroid carcinoma, in particular, the ground-glass nuclei. Pathologists in Russia, having experience with thyroid tumors from radiocontaminated areas, pointed out the "low quality of histological specimens, impeding assessment of nuclei" (2).

False-positive diagnosis of TC was not excluded after cytological and histological examination. If a thyroid nodule is found during ultrasonic screening, a fine-needle aspiration biopsy (FNA) is usually performed. Thyroid FNA cytology is known to be accompanied by a certain percentage of inconclusive results (so-called grey zone): figures about 10–20 % are reported from modern clinical centres (9) but in the former Soviet Union percentage was higher, one of the causes being absence of modern literature in hospitals and laboratories. Data about sensitivity of the FNA in detecting post-Chernobyl childhood TC can be found in the dissertation of A.Iu. Abrosimov (1) a well-known specialist in this area: "In a definite or presumptive form, diagnosis of carcinoma was established in 161 from 238 cases", whereas papillary carcinoma was diagnosed correctly by FNA in 69,5 % and its follicular variety - only in 36,5 % of cases. As it follows from the context, presumptive diagnoses were included among correctly diagnosed cases. After receiving a cytological report in a presumptive form ("atypical cells" or "suspicion of carcinoma"), depending on the nodule size, a lobectomy or subtotal thyroid resection is performed, and the surgical specimen is sent for pathological examination. Histopathological differential diagnosis of thyroid nodules is again a problematic area. High quality of specimens, required for adequate evaluation of nuclear changes in papillary carcinoma, was not always achieved at that time. For search and evaluation of malignancy criteria of a minimally-invasive follicular carcinoma (capsular and vascular invasions) great number of sections can be needed, which have not always been made. Besides, it is known from praxis that after a radical removal of a presumed carcinoma, a pathologist can be inclined to confirming malignancy even in case of some uncertainty.

Moreover, in the 1990s some diagnostic criteria of TC were hardly known in the former Soviet Union, and were not mentioned by Russian-language handbooks and monographs in use at that time (6, 19). The minimally-invasive follicular carcinoma and its diagnostic criteria were absent in Russian-

language literature. One of the most significant diagnostic criteria of papillary carcinoma – ground-glass or cleared nuclei – was mistranslated as "watch-glass nuclei molded together" (yadra v vide priertykh chasovykh stekol) and presented by the most authoritative Russian-language handbook of tumor pathology (19) as a sign not only of papillary, but also of follicular TC, for which it is not characteristic. Description of this phenomenon in the handbook does not agree with international literature. Nuclear changes, characteristic of papillary carcinoma, are not visible in the illustrations of this handbook. Even less understandable comparison with a sand-glass (another mistranslation of the "ground-glass") can be encountered.

In the "Atlas of human tumor pathology" (23) recently edited in Russia, the following is stated with reference to thyroid nodules: "In severe dysplasia there appear cell groups with clearly visible atypia. Therefore, 3rd grade dysplasia is considered as an obligate pre-cancer, which histologically is hardly distinguishable from carcinoma *in situ*". Nuclear atypia (enlargement, hyperchromatism, pleomorphism) is not regarded in modern literature as a malignancy criterion of follicular and papillary thyroid nodules, and the concepts of carcinoma *in situ* and dysplasia are not applied to them (26). Cases of false-positive TC diagnosis, caused by misinterpretation of nuclear atypia as a malignancy criterion, are known. Follicular and solid varieties of papillary TC prevailed in children and adolescents after the CA (4, 21). Diagnosis of these subtypes of papillary carcinoma is largely based on the nuclear criteria, inadequate assessment of which can result in false-positive conclusions, for example, in case of well-differentiated tumors of uncertain malignant potential (12) or benign papillary nodules (18,20).

Remarkable observations about post-Chernobyl attitude to thyroid nodules can be found in Russian-language literature: "Practically all nodular thyroid lesions in children, independently of their size, were regarded as potentially malignant neoplasms, requiring urgent surgical operation" and "Aggressiveness of surgeons contributed to the shortening of the minimal latent period" (24). Obviously, it was not the matter of true latency shortening but of early detection. Data about verification by expert commissions of post-Chernobyl pediatric TC in Russia provided further evidence for false-positivity: "As a result of histopathological verification, diagnosis of TC was confirmed in 79,1 % of cases (federal level of verification – 354 cases) and 77,9 % (international level – 280 cases)" (1). Obviously, false-positive diagnoses remained undisclosed in cases not covered by verification.

Another evidence in favor of false-positivity: incidence of pediatric TC in Bryansk region, the most radiocontaminated area in Russian Federation, having increased from zero (1986-89) up to 9 cases in 1994 and 8 in 1995, decreased back to zero in 2001 and 1 case yearly in the subsequent 2002-2003 years (24) disagreeing with prognoses that radiation-induced TC morbidity in Bryansk region inhabitants, who had been children or adolescents at the time of CA, would grow nearly exponentially until 2021 and beyond (28). Analogous data were presented also from Belarus (10). These figures can be explained by false-positivity in the early period after CA with subsequent improvement of diagnostic accuracy. In this connection, lack of statistically significant TC increase in children born after the CA can be understood: the data pertaining to them originated from a later period, "oncological alertness" affected these children to a lesser degree, and there were no motives to artificially enhance the figures.

Research on post-Chernobyl pediatric TC is in a cul-de-sac: the data documenting its dramatic increase are felt to be inflated, but to prove it with figures would be not easy today. Arguments presented in this article allow concluding that high figures were at least in part caused by improved detection of thyroid nodules with occasional false-positive diagnoses of malignancy. Besides, latent carcinomas and borderline

lesions, including well-differentiated tumors of uncertain malignant potential (12) found by echo-screening and diagnosed as malignancies, could have additionally contributed to the high incidence figures. Clarification of this issue, retrospective correction of false-positive diagnoses and their preclusion in future are indicated because of the overtreatment risk. The following treatment is recommended to the children with supposed radiation-induced carcinoma: "radical thyroid surgery including total thyroidectomy combined with neck dissections followed by radioiodine ablation" (10); "Thyroidectomy and lymph node dissection. Careful and complete removal of the lymph nodes is of great clinical relevance" (25).

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MUDr. Sergej V. Jargin
Per. Clementovski 6-82
115184 Moscow, Russia
E-mail: sjargin@mail.ru

ERRATUM

V minulém čísle časopisu (*Čes.-slov. Patol.*, 45/1, 2009, s. 14–18) byla uveřejněna práce Makovický Pe., Makovický Pa., Maxová M.: „Možnosti diagnostiky celiakie v bioptické praxi“. Autory této práce jsou pouze Makovický Pe. a Makovický Pa. Ing. M. Maxová z IKEM Praha není spoluautorkou a redakce se jí za chybné uvedení omlouvá.