Human Pathology (2018) 74, 170–177

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Human PATHOLOGY

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Original contribution

Characteristics of cribriform morular variant of papillary thyroid carcinoma in post-Chernobyl affected region☆,☆☆,★

Alfred King-yin Lam MBBS, PhD, FRCPath, FRCPA[a,*], Mikhail Fridman MD, PhD[b]

[a]Discipline of Pathology, School of Medicine and Menzies Health Institute Queensland, Griffith University, Gold Coast 4222, Australia
[b]Republican Centre for Thyroid Tumors, Nezavisimosty Av., 64, 220013 Minsk, Belarus

Received 8 November 2017; revised 27 December 2017; accepted 2 January 2018

Keywords:
Thyroid;
Papillary thyroid carcinoma;
Cribriform morular;
Variant;
Radiation;
Pathology;
Chernobyl

Summary The aim is to study the characteristics of cribriform morular variant of papillary thyroid carcinoma (CMV-PTC) in patients living in the radiation-affected area of Belarus. The clinical and pathological features of 35 patients with CMV-PTC from Belarus were studied and compared with those of conventional papillary thyroid carcinoma diagnosed in the same period. The patients with CMV-PTC were all females and were younger at presentation (mean age = 24) than those with conventional papillary thyroid carcinoma. Familial adenomatous polyposis (FAP) was identified in 20% of the patients with CMV-PTC. The majority of the CMV-PTCs (29/35; 83%) were staged as pT1 and were less advanced than conventional papillary thyroid carcinoma. There was no evidence of lymph node metastases or distant metastases. CMV-PTCs were positive for β-catenin, APC (adenomatous polyposis coli) and p53 proteins. No psammoma bodies were identified on microscopic examination. Over a median follow-up of 9 years, all the patients were alive, and there was no cancer recurrence or mortality related to the thyroid cancer. To conclude, CMV-PTC in patients in the radiation-affected region behaves in an indolent fashion. They had distinctive features that are different from patients with conventional papillary thyroid carcinoma living in the same region.
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1. Introduction

In 1990, Chan and Loo from Hong Kong reported the first case of cribriform morular variant of papillary thyroid carcinoma (CMV-PTC) in the English literature [1]. This variant of papillary thyroid carcinoma was first accepted as a variant of papillary thyroid carcinoma in the third edition of the World Health classification (WHO) of tumours of endocrine organs published in 2005 [2]. It was labelled as "cribriform carcinoma." In the current edition of the WHO classification of endocrine tumours in 2017, the tumour is called "cribriform-morular" variant of papillary thyroid carcinoma [3,4]. Belarus is a country highly affected by an accident at the Chernobyl nuclear power plant in Ukraine on April 26, 1986. Radiation is a known predisposing factor for thyroid cancer. Studies have reported that these thyroid cancers in radiation-affected areas affect mainly children,

☆ Competing interests: There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.
☆☆ Funding/ support: The research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.
★ ORCID: 0000-0003-2771-564X
* Corresponding author at: School of Medicine, Griffith University, Gold Coast Campus, Queensland 4222, Australia.
E-mail address: a.lam@griffith.edu.au (A. K. Lam).

https://doi.org/10.1016/j.humpath.2018.01.006
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adolescents and young adults and have different characteristics when compared to the thyroid cancers noted in non–radiation-affected areas [5,6].

CMV-PTC is uncommon and affects mainly young adults [3,4]. Survival data from the literature for patients with CMV-PTC were derived mainly from case reports and small reported series from non–radiation-affected areas [7]. The clinical behaviour of the CMV-PTC in the radiation-exposed region have not been studied. In this study, we analysed the clinical and pathological features of all the CMV-PTC reported over the past 23 years in Belarus. We also compared the features of them with the conventional papillary thyroid carcinoma diagnosed in the same period. In addition, the features of CMV-PTC noted in the population were compared with CMV-PTC reported in the English literature.

2. Subjects and methods

The clinical presentation, pre-operative ultrasonic examination and fine needle aspiration, surgical treatment, postoperative adjuvant therapy, recurrence and long-term survival data of the patients with CMV-PTC were studied. The Review Board of the Minsk Municipal Clinical Hospital for Oncology in Minsk for Belarus approved the study. The patients with thyroid cancer gave the consents at the time of surgery to share epidemiological, clinical and pathological data for further investigation. The privacy rights were obtained for experimentation with human subjects. The location, size and histological features of the tumours were noted on pathological examination. The Tumour–Lymph nodes–Metastasis (TNM) staging was determined according to the 8th edition of AJCC (American Joint Committee on Cancer) Cancer staging manual [8].

The authors have reviewed and confirmed the diagnosis of CMV-PTC diagnosed in the Department of Pathology of Minsk Municipal Clinical Hospital for Oncology in Belarus between the years 1993 to 2015 using the criteria of the *WHO Classification of Tumours of Endocrine Organs* [3,4]. The laboratory in the Department of Pathology was set up in the year 1995. The same team of pathologists diagnosed all the thyroid carcinomas in Belarus. Amongst these, patients with papillary thyroid carcinomas having the features of CMV-PTC were identified for further clinical and pathological studies. After the histological review, a block from each patient with representative CMV-PTC morphology was selected for immunohistochemical analysis. The antibodies used were against β-catenin (ThermoFisher Scientific, Waltham, MA, USA), APC (adenomatous polyposis coli; ThermoFisher Scientific), p53 (Dako, Agilent, Santa Clara, CA, USA) and Ki-67 (ThermoFisher Scientific). The antibodies used were pre-diluted. The deparaffinised sections were treated with buffer and stained according to the protocols recommended by the companies. Blocks of colonic adenoma and colonic adenocarcinoma from patients with polyposis coli were used as positive controls for staining of β-catenin and APC. A block of anaplastic thyroid carcinoma was used as positive control for Ki-67 and p53. In addition, a block of conventional papillary thyroid carcinoma was used to compare the staining of CMV-PTC in β-catenin and APC staining.

The data of the patients with CMV-PTC and conventional PTC diagnosed in the same Belarus hospital were entered in a database for statistical analysis. Statistical analysis was made with the Statistical Package for Social Sciences for Windows (version 24.0, IBM, New York, NY, USA). Significance level was taken at $P < .05$.

We have previously reviewed the 129 cases of CMV-PTC in the literature [7]. No evidence was present that these patients were from areas affected by post-Chernobyl radiation or previously treated with external irradiation. In this study, we compared the features of the CMV-PTC in radiation-affected areas with those of the 129 reported cases in the literature.

3. Results

There were 35 patients with CMV-PTC noted (Table 1). In the same period, there were 21 355 papillary thyroid carcinomas noted in the same institution. Thus, the variant accounted for 0.16% of papillary thyroid carcinomas diagnosed over the 23-years study period in the country of Belarus. In addition, in the same period, there were 14 353 patients with conventional papillary thyroid carcinoma and 7 002 patients with follicular, diffuse sclerosing, tall cell and other variants.

All the patients with CMV-PTC were females. On the other hand, the female-to-male ratio of conventional papillary thyroid carcinoma was 4.9 to 1. The difference in gender distribution between the CMV-PTC and conventional papillary thyroid carcinoma was significant ($P = .0001$). The mean and median age of patients with CMV-PTC at presentation was 24 years and 21 years, respectively (range = 15-52 years). The patients with CMV-PTC most often presented in the second decade of life (age = 10-19; n = 15). Seventy-four percent (n = 26) of the patients were under the age of 30 years at presentation. In contrast, the mean and median age of patients with conventional papillary thyroid carcinoma was 46 years and 48 years, respectively (range = 5 to 93). Only 15% of the conventional papillary thyroid carcinoma were younger than 30 years at presentation. The difference in age distribution between the 2 variants of papillary thyroid carcinoma was significant in this population ($P = 0.0001$).

All the patients with CMV-PTC were asymptomatic. The thyroid nodules in these patients were detected during the check-up by general practitioners. They were often diagnosed as benign lesions by ultrasonic examination, with 86% (30/35) being reported as benign thyroid nodules. The remaining 14% (n = 5) of patients were reported as suspicious for cancer.

Of the 35 patients with CMV-PTC, 20% (n = 7) had familial adenomatous polyposis (FAP) or FAP-associated syndromes. All but 1 had T1 thyroid cancers. Five of these 7 patients had single or multiple colonic polyps revealed during 1 to 185

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