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Three Synchronous Primary Extranodal Mantle Cell Lymphomas Involving Torus Tubarius, Posterior Nasopharynx, and Base of the Tongue 65 Years After Treatment of Chronic Sinusitis with Nasopharyngeal Radium Irradiation

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Data Collection B
Statistical Analysis C
Data Interpretation D
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Conflict of interest: None declared

Patient: Male, 81
Final Diagnosis: Mantle cell lymphoma
Symptoms: Difficulty in swallowing and pain in the right ear
Medication: —
Clinical Procedure: Otorhinolaryngology panendoscopy • biopsy of the tumors
Specialty: Otolaryngology

Objective: Rare disease

Background: Radiation, specifically ionizing radiation, causes broad-spectrum gene damage, including double-strand DNA breaks, single DNA strand breaks, cross links, and individual base lesions, thus causing chromosomal translocations, deletions, point mutations, and, consequently, various types of cancer. Radiation also causes genomic instability in cells, which enhances the rate of mutations in the descendants of the irradiated cell after many generations of normal replications.

Case Report: We report the first case of mantle cell lymphoma of the torus tubarius, and the first CD10-positive mantle cell lymphoma of the Waldeyer's ring. Mantle cell lymphoma appeared 65 years after treatment of chronic sinusitis with nasopharyngeal radium irradiation.

Conclusions: On the basis of the medical literature about atomic bomb survivors, nuclear plant workers, and radiologists exposed to radiation, and our case, we conclude that radiation can, in a very small percentage of exposed individuals, cause non-Hodgkin lymphoma: in 0.24% of atomic bomb survivors and in at least 0.13% of the patients treated with nasopharyngeal radium irradiation.

Non-Hodgkin lymphoma can occur many decades after radiation exposure, and individuals treated with nasopharyngeal radium irradiation, usually in their childhood, need continuing follow-up.

MeSH Keywords: Eustachian Tube • Lymphoma, Mantle-Cell • Nasopharyngeal Neoplasms • Radium

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Background

Waldeyer's ring – the palatine tonsils, nasopharyngeal tonsil, tubal tonsils, and lingual tonsil – contains abundant lymphoid tissue that safeguards the entrance to the alimentary and respiratory tracts. It can secondarily be involved by the spread of non-Hodgkin or Hodgkin lymphomas from other primary places, but the Waldeyer's ring is more frequently a primary rather than a secondary site of non-Hodgkin lymphoma [1]. Primary lymphomas of the Waldeyer's ring account for 5% to 10% of all lymphomas and more than 50% of all primary extranodal lymphomas of the head and neck [2]. The tonsil is the most frequently involved site, accounting for more than half of Waldeyer's ring lymphomas, followed by the nasopharynx and the base of the tongue [3]. Lymphoid tissue in the Waldeyer's ring is not acquired, and the same types of non-Hodgkin lymphomas that occur in the lymph nodes also occur in the Waldeyer's ring. Diffuse large B cell lymphoma is the most common type, accounting for 60% to 84% of Waldeyer's ring lymphomas, and less common types include follicular lymphoma, Burkitt's lymphoma, mantle cell lymphoma, and extranodal marginal zone lymphoma [3]. The most common primary lymphomas of the nasopharynx are mantle cell lymphoma, follicular lymphoma, and small lymphocytic lymphoma [4]. To the best of our knowledge, mantle cell lymphoma of the torus tubarius has not been previously reported.

The cardinal feature and one of the driving forces of mantle cell lymphoma is the translocation t(11;14)(q21;q21), by which the CCND1 gene from chromosome 11 is juxtaposed with the immunoglobulin heavy chain gene (IgH) on derivative chromosome 14. Since the IgH gene is active in lymphocytes, overtranscription of the CCND1 gene results in overexpression of the cyclin D1 protein (bcl-1), which keeps cells in permanent S-phase of the mitotic cycle. The CCND1 gene is a weak oncogene and is only a primary event in the pathogenesis of mantle cell lymphoma. Additional chromosomal abnormalities may include: chromosome 13 abnormalities (deletions more common than gains), del 1p, gains of 3q, 10p aberrations, del 17p, and changes in chromosomes 7, 8, 9, 12, 15, and 21 [5]. Comparative genomic hybridization and analysis using single-nucleotide polymorphism arrays have confirmed that mantle cell lymphoma is genetically highly complex and shows a large number and variety of copy number alterations [5]. Areas of chromosomal gain occur in 20–50% of mantle cell lymphomas and include 3q, 8q, 10q, 15q, and 18q, while losses occur in 30–50% of mantle cell lymphomas and include 1p, 6q, 8p, 9p, 9q, 11q, 13q 17p, and 20q. [5]. Translocations can be detected by chromosomal study and FISH study, while overexpression of bcl-1 can be easily detected by immunohistochemistry. Flow cytometric study of the fresh tissue detects light chain restriction and characteristic immunophenotypic features of mantle cell lymphoma cells – expression of the

T-cell marker CD5 together with expression of the pan B-cell markers CD19, CD20, and CD22 – and enables differentiation from morphologically similar B cell chronic lymphocytic leukemia. Mantle cell lymphoma cells express FMC-7 marker and not CD23, while B cell chronic lymphocytic leukemia cells express CD23 and not FMC-7. Expression of CD20 and surface immunoglobulin light chains is weak in B cell chronic lymphocytic leukemia and strong in mantle cell lymphoma. Regarding morphology, mantle cell lymphoma cells are small to intermediate-sized lymphocytes with scant cytoplasm and nuclei with irregular nuclear contours, mature dark chromatin, and no nucleolus. Mantle cell lymphoma involves lymph nodes in 3 patterns. The diffuse pattern is the most common (75–80% of cases), the nodular pattern (vague nodules that obliterate follicles and germinal centers) occurs in about 20%, and the mantle zone pattern (broaden bcl-1-positive mantle zones around reactive germinal centers) appears in about 1% of patients [5]. Similar patterns can also be seen in extranodal mantle cell lymphomas.

Ionizing radiation causes a broad spectrum of DNA damage, including individual base lesions, crosslinks, and single-strand and double-strand DNA breaks [6], which can cause various types of cancer. When 2 single-strand breaks occur on opposite DNA strands, a double-strand break is created, which is one of the basic lesions responsible for chromosomal abnormalities, including translocations [6]. Radiation can also induce a type of genomic instability in cells that enhances the rate at which mutations and other genetic changes arise in the descendants of the irradiated cell after many generations of replication [7].

Case Report

An 81-year-old man noticed difficulty in swallowing off and on for approximately 9 months. He underwent esophagogastros-copy, which found no clear-cut abnormality, and he was subsequently submitted for esophageal dilation. However, dysphagia persisted, and 3–4 months later, he noted pain in the right ear. Chronic ear disease, including left-sided ossicular erosion, was his long-standing problem, but the right-sided effusion was new. Otorhinolaryngology pan endoscopy revealed 3 separate tumors in the Waldeyer's ring. Swelling (tumor) of the posterior-medial pad of the right Eustachian tube (torus tubarius) measured superior to inferior 15 mm x 7 mm and was covered with granular mucosa (Figure 1).

Palatopharyngeal mucosa on the right had an area of lymphatic tag (morphologically similar to the after-tonsillectomy tag) that measured 15 mm by 10 mm. This area was not friable and was PET (positron emission tomography)-negative. There was a slightly exophytic lesion on the right base of the tongue that measured 15x15 mm. It was PET-positive and was

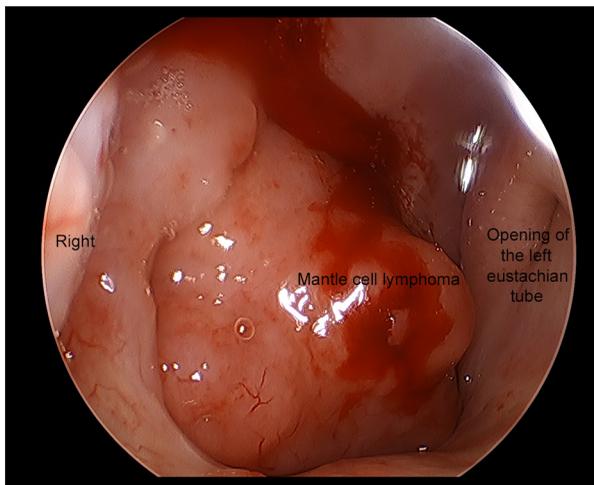


Figure 1. Mantle cell lymphoma tumor with a granular surface has replaced the posterior-medial pad of the right torus tubarius. Endoscopic photograph of the nasopharynx with a 0-degree telescope trans-nasally.

not friable. The 3 tumors were non-contiguous. Physical examination showed that neck lymph nodes were not enlarged nor were any other external lymph nodes. CT (computerized tomography) of the soft tissue of the neck confirmed absence of enlarged lymph nodes and demonstrated a 2.2×2.2 cm tumor in the region of the right fossa of Rosenmüller and fullness (tumor) in the posterior most inferior base of the right tongue.

PET/CT scan of the whole body showed no evidence of enlarged lymph nodes or enlarged spleen. A PET-positive hot-spot appeared only in the nasopharynx (a 2.4-cm mass) and right base of the tongue (a 0.9-cm mass). Colonoscopy showed no evidence of polyps. Bone marrow biopsy was not performed because it was not indicated for this patient according to the contemporary oncology guidelines.

The patient reported that when he was about 15 years of age, he had had persistent sinus infections with drainage to the point that he had missed a significant part of his school year. His sinusitis was treated sometime during 1951–1952 by insertion of radium rods in both nostrils. The therapy resulted in significant improvement of his chronic sinus symptoms, and he was healthy for the next 66 years until dysphagia occurred.

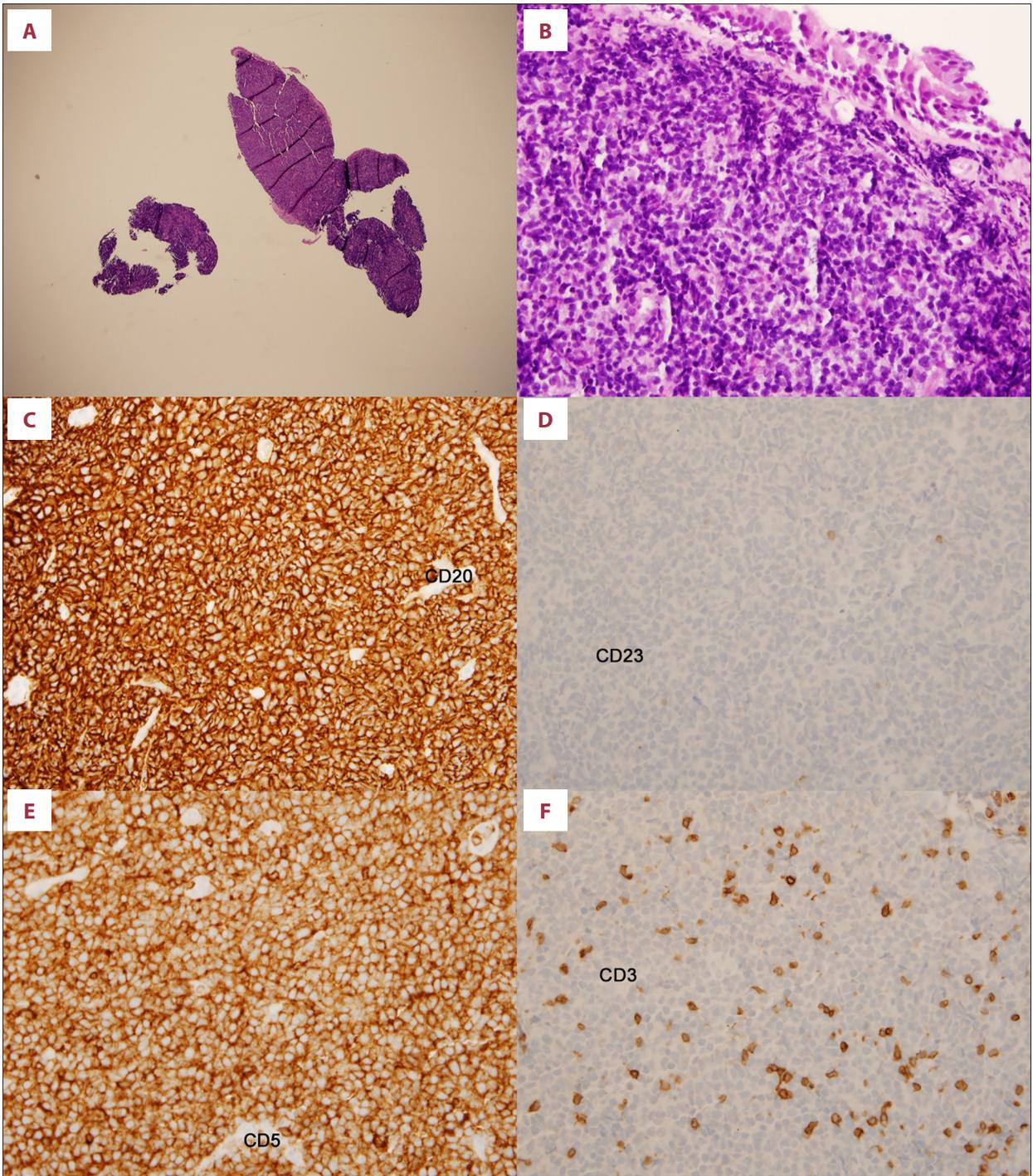
Hematoxylin and eosin stained section of the torus tubarius tumor biopsy demonstrated total effacement of the normal architecture by dense diffuse infiltration with small-to-intermediate size lymphocytes with irregular nuclei, dark chromatin without nucleoli, and very scant cytoplasm (Figure 1). There was no evidence of prolymphocytes, blastic cells, or large pleomorphic cells. There were 2 mitoses/10 high-power fields (magnification 400 times). Malignant cells were positive for CD20, CD5, bcl-1, SOX11, and bcl-6, and negative for CD23.

The morphology of malignant cells, the characteristic immunophenotype, and genetic study established a diagnosis of mantle cell lymphoma. Mantle cell lymphoma cells were also positive for CD10 by immunoperoxidase stain (Figures 2J, 3B, 4B) and by flow cytometric immunophenotyping. Proliferation fraction (by Ki-67) was 60% in torus tubarius (Figure 2) and posterior nasopharynx mantle cell lymphomas, and 10–15% in the base of the tongue mantle cell lymphoma.

FISH study documented Bcl-1/IgH rearrangement in 100% of the nuclei. The BCL-6, BCL-2, and MYC rearrangements were negative. Flow cytometric study revealed immunoglobulin lambda light chains restricted B cells, dim expression of CD5 on mantle cells, and expression of CD10 on mantle cells. CD23 was not expressed. Chromosomal study was not contributory because mitoses were not obtained in the cell culture.

Discussion

In our patient, mantle cell lymphoma was morphologically typical and similar in all 3 locations. The pattern was diffuse and there was no evidence of blastic or pleomorphic variants. FISH studies documented the characteristic t(11q21;14q21) translocation, with no evidence of double-hit lymphoma. Immunophenotype was also characteristic and diagnostic for mantle cell lymphoma. However, malignant cells also expressed germinal center cell markers CD10 and bcl-6. CD10-positive mantle cell lymphomas are rare and account for about 3.8% of mantle cell lymphomas [8]. According to some authors, compared with CD10-negative mantle cell lymphomas, CD10-positive mantle cell lymphomas more often have diffuse growth pattern, blastoid/pleomorphic morphology, and bcl-6 expression [8]. When CD10-positive mantle cell lymphomas exhibit a high proliferation fraction (more than 60% by Ki-67), blastoid/pleomorphic morphology, or high International Prognostic Index, the patients have worse prognosis [8]. However, some authors state that CD10-positive mantle cell lymphomas do not show significant differences in clinical or pathological features, frequency of immunoglobulin somatic hyper mutation, or clinical outcome compared to CD10-negative mantle cell lymphomas [9]. These authors think that CD10 expression only means a distinct germinal center signature, but without clinical or biological implications [9]. CD10-positive mantle cell lymphoma of the Waldeyer's ring has not been previously reported. We have not used loss of heterozygosity testing to study whether 3 mantle cell lymphomas on 3 locations in the Waldeyer's ring are 3 different clones (tumors) or 1 clone (one tumor). Since expression of CD10 in mantle cell lymphoma is very rare, and all 3 tumors expressed CD10 (Figures 2–4) and bcl-6, we presume that it is 1 tumor that disseminated/homed [4] to the 3 out of 4 tonsils of the Waldeyer's ring.



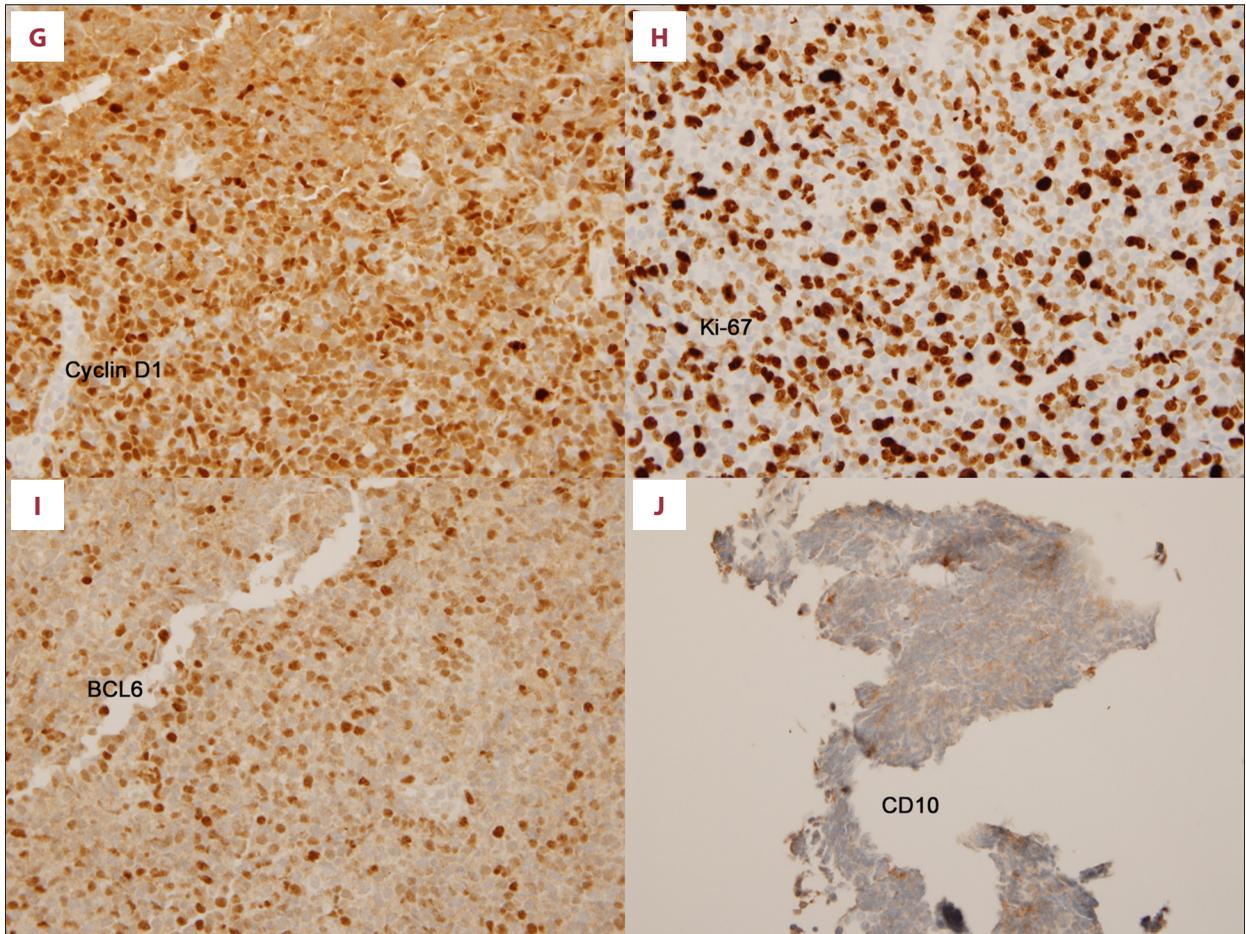


Figure 2. Mantle cell lymphoma of the right torus tubarius. Immunohistochemistry (original magnification $\times 400$). (A) Hematoxylin and eosin staining, original magnification times 20, (B) times 400, (C) lymphoma cells were positive for CD20, (D) lymphoma cells were negative for CD23, (E) lymphoma cells were positive for CD5, (F) lymphoma cells were negative for CD3, (G) lymphoma cells were positive for cyclin D1, (H) the majority of lymphoma cells were positive for Ki-67, (I) lymphoma cells were positive for BCL6, (J) lymphoma cells were positive for CD10.

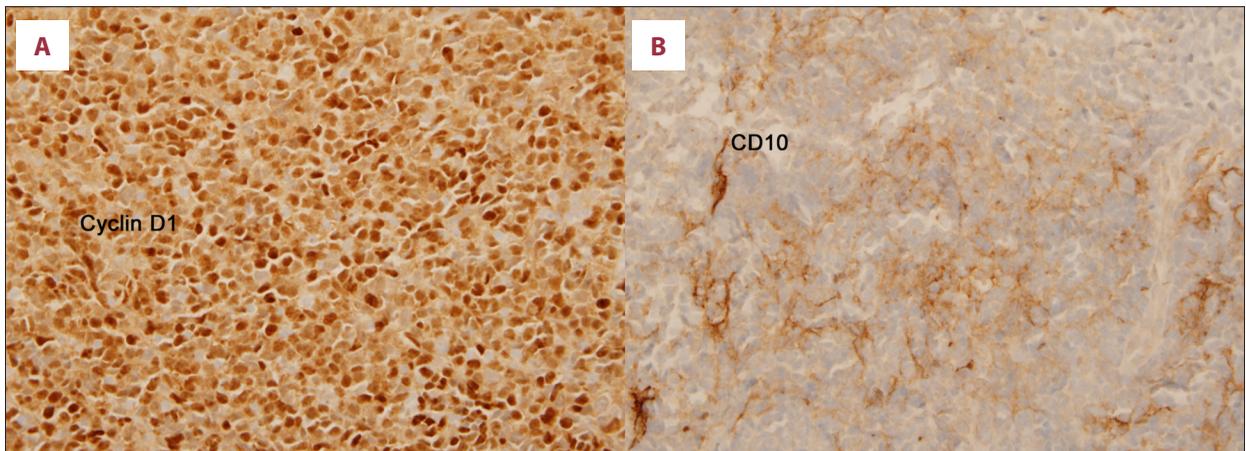


Figure 3. Mantle cell lymphoma of the nasopharynx. Immunohistochemistry (original magnification $\times 400$). (A) lymphoma cells were positive for BCL1, (B) lymphoma cells were positive for CD10.

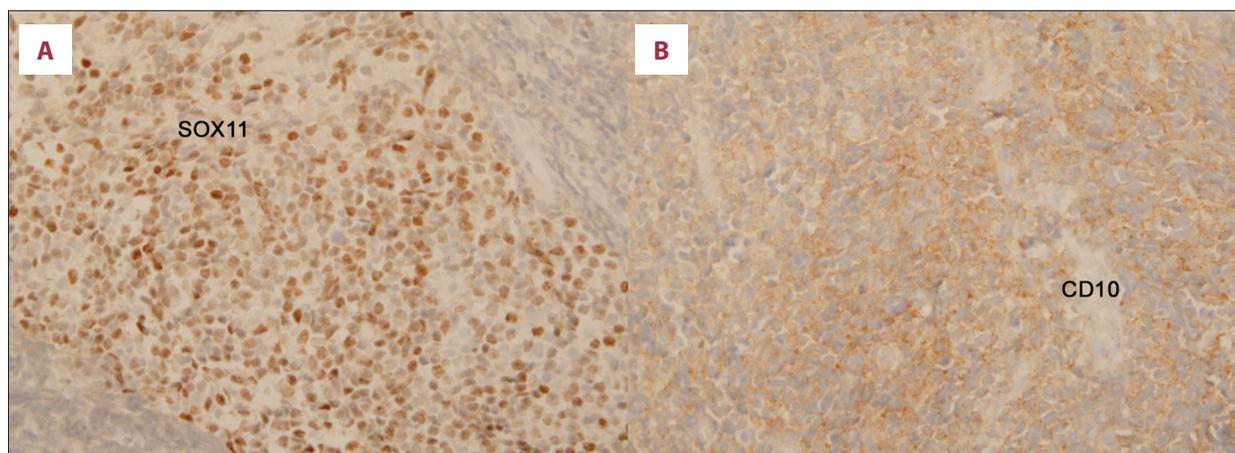


Figure 4. Immunohistochemistry (original magnification x 400) of mantle cell lymphoma of the base of the tongue. (A) Lymphoma cells were positive for SOX11, (B) lymphoma cells were positive for CD10.

From 1940 through the mid- to late 1960s, nasopharyngeal radium irradiation was used to treat hearing loss, chronic otitis media, aerotitis media in submariners and aviators, middle ear barotrauma, sinusitis, recurrent tonsillitis, and asthma [10]. The aim was to reduce by irradiation local hyperplasia (swelling) of lymphoid tissue and thus allow the middle ear to drain through the Eustachian tube, thereby preventing chronic ear infections that could lead to hearing loss [10]. An estimated 500 000 to 2 000 000 civilians, mainly children, and more than 8000 World War II servicemen were treated with nasopharyngeal radium irradiation [10]. Treatment consisted of bilateral insertion of an applicator with a platinum capsule of radium through each nostril, with placement of the radium near the Eustachian tube opening for 8–12 minutes. Three treatments were administered at 2- to 3-week intervals, and a second course of 3 treatments was occasionally given [10]. Most radiation from nasopharyngeal radium was in the form of beta particles; therefore, the highest dose of radiation was delivered to the soft tissue of the nasopharynx. Radiation doses to nearby organs were estimated on the basis of bilateral use in an adult of 50 mg of radium sulfate in a 0.5-mm platinum capsule for 12 minutes per session for 3 sessions [10]. Estimation of radiation was 2000 rads to the mucosal lining of the nasopharynx, 24 rads to the pituitary gland, 5 rads to the brain, and 2 rads to the thyroid [10]. Radiation of 2000 rads is a very high radiation. The cancer incidence after nasopharyngeal radium irradiation was very low, but higher than in unexposed individuals. Based on a cohort study in Maryland USA of 904 exposed and 2021 unexposed persons during 1943–1960, the risk for all head and neck cancers combined was statistically significantly higher in the exposed group [11]. However, the number of cancers was low (3 brain cancers and 1 soft palate cancer) and statistical significance was achieved because of the large number of studied individuals. A retrospective cohort study of all-case and cancer-related mortality in the Netherlands [12] compared 5358 Dutch patients treated with nasopharyngeal

radium irradiation, mostly in childhood, and 5265 frequency-matched non-exposed subjects [12]. Average doses to the nasopharynx, pituitary gland, brain, and thyroid gland were 275, 10.9, 1.8, and 1.5 rads (cGy), respectively. This study demonstrated excess deaths from hematopoietic malignancies with standardized mortality ratio for non-Hodgkin lymphomas 2.6 (confidence interval 1.0 to 5.3), leukemia 1.6, and multiple myeloma 2.8. There were 7 deaths from non-Hodgkin lymphomas in 5358 patients exposed to nasopharyngeal radium irradiation, yielding a mortality rate was 0.13%. Taking in account the outcome of non-Hodgkin lymphomas in that period (1945–1981), the prevalence of non-Hodgkin lymphomas was very close to the mortality rate, and possibly slightly higher. The same group of authors 1 year later confirmed this notion by studying cancer incidence, demonstrating increased risks for malignancies of lymphoproliferative and hematopoietic origin, with a standardized incidence ratio 1.9 in the patients treated with nasopharyngeal radium irradiation follow-up periods of 18–50 years [13]. The prevalence of lymphomas [14] – Hodgkin lymphomas and non-Hodgkin-lymphomas – as classified as suggested by Rappaport [15], in atomic bomb survivors exposed to more than 100 rads was 25.49 per 10 000 Hiroshima population (0.25%). Analysis of data on the incidence of lymphoma in the “Life-Span Study cohort of atomic bomb survivors for time period 1950 to 1987,” identified 229 lymphoma cases out of 93 796 survivors, or 0.24% [16].

The etiology of mantle cell lymphoma is unknown. Established risk factors for non-Hodgkin lymphomas are heredity, infectious agents, immunosuppression, and autoimmune diseases, while suggestive risk factors are genetic polymorphism, exposure to agricultural agents, exposure to hair dyes, and exposure to immunomodulatory therapies [5]. It is unequivocal that radiation can cause acute myeloid leukemia [17–19], epithelial cell cancers [20], hepatic angiosarcoma [21], and other malignancies. Regarding non-Hodgkin lymphomas, there is some doubt that

lymphomas are rarely, if ever, found to be caused by ionizing radiation [22], a view supported by an epidemiologic study [23]. We do not think that the absence of a study clearly demonstrating a dose-response relationship for the development of non-Hodgkin lymphomas [22] excludes a very small percentage of exposed patients developing non-Hodgkin lymphomas resulting from previous radiation exposure. Radiation can break chromosomes, create rearrangements, cause deletion and mutations, and thus can form drivers of tumor growth, and it is thus plausible that radiation can yield drivers of non-Hodgkin lymphoma growth. There is convincing data in the medical literature (as cited here) that radiation can cause non-Hodgkin lymphoma, although in only a very low percentage of exposed individuals. Chromosome aberrations in B lymphocytes were demonstrated in atomic bomb survivors [24]. Epidemiologic studies of atomic bomb survivors demonstrated increased risk of lymphoma in males [14], with a weak suggestion of radiation dose response for non-Hodgkin lymphoma in men, and no indication of such an effect among women [25]. Epidemiologic study of radiologists [19], cohort studies of patients with nasopharyngeal radium irradiation [10–13], and single case reports [26–28], including our patient, support a causal relation between the non-Hodgkin lymphomas and ionizing radiation. The percentage of patients who develop non-Hodgkin lymphoma after radiation exposure is very low, and non-Hodgkin lymphomas can occur many decades after exposure (65 years in our patient, 62 years after the atomic bomb [27] in Hiroshima), which make epidemiologic studies and cause-consequence relation difficult to prove by statistical methods. We presume that in our patient, the nasopharyngeal radium irradiation did not directly (at the time when applied) cause translocation t11;14. However, if translocation had happened, which is unlikely, the development of lymphoma was delayed for 65 years until additional chromosomal changes appeared. We believe that the following

scenario is more probable: According to the literature, we assume that the nasopharyngeal irradiation caused genomic instability in Waldeyer's ring cells and that mantle cell translocation occurred in the descendants of the irradiated cells [7] after many generations of normal replications throughout 65 years. If our patient's lymphoma was not associated with nasopharyngeal irradiation, it would probably appear as peripheral lymphadenopathy and not in torus tubarius, where it has never been reported.

Conclusions

We report the first case of mantle cell lymphoma of the torus tubarius and the first CD10-positive mantle cell lymphoma of the Waldeyer's ring, and conclude on the basis of the medical literature and our case that radiation can cause non-Hodgkin lymphoma in a very small percentage of exposed individuals – in at least 0.13% of patients treated with nasopharyngeal radium irradiation and in 0.24% of atomic bomb survivors. Non-Hodgkin lymphoma can occur many decades after radiation exposure, and individuals treated with nasopharyngeal radium irradiation (usually in their childhood) need continuing follow-up.

Department and Institution where work was done

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Conflict of interest

None.

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