Case Reports

Artur Bocian[1], Janusz Kopczyński[2], Piotr Rieske[5], Sylwester Piaskowski[5], Janusz Słuszniak[1], Dorota Kupnicka[6], Stanisław Góźdź[3], Aldona Kowalska[4], Jacek Sygut[2]

Simultaneous Occurrence of Medullary and Papillary Carcinomas of the Thyroid Gland with Metastases of Papillary Carcinoma to the Cervical Lymph Nodes and the Coinciding Small B-Cell Lymphocytic Lymphoma of the Lymph Nodes – a Case Report

[1]Department of Surgery,
[2]Department of Pathology,
[3]Deparment of Chemotherapy,
[4]Department of Endocrinology, Holy Cross Cancer Center, Kielce,
[5]Department of Molecular Pathology and Neuropathology, Chair of Oncology,
[6]Department of Tumor Pathology, Medical University, Łódź

We report a case of a simultaneous occurrence of medullary and papillary carcinomas of the thyroid gland with metastases of a papillary carcinoma to the cervical lymph nodes and a concurrent small B-cell lymphocytic lymphoma revealed in the lymph nodes examined in a 71-year-old woman. The diagnosis was based on microscopic examination of surgical specimens and supported by immunohistochemistry. Additionally, *P53* and *RET* mutation analysis was performed. In this case, the coincidence of medullary and papillary carcinomas of the thyroid gland may account for a true composite tumor. The coexistence of a small B-cell lymphoma in our patient may be explained by irradiation treatment undergone during the adolescence.

Introduction

A simultaneous occurrence of two different carcinomas stemming from embryologically different cells in the thyroid gland is identified very rarely. To date, there have been a few cases described in the literature of the occurrence of both a medullary and papillary carcinoma of the thyroid involving different areas of the same gland. However, to our best knowledge, the coexistence of a medullary and papillary carcinoma of the thyroid with a small B-cell lymphoma in the removed glands has not been hitherto reported.

In this report we describe a case of a thyroid carcinoma demonstrating both types – a medullary carcinoma and papillary carcinoma – with metastases to the lymph nodes, and a simultaneous coexistence of a malignant lymphoma arising from small B cells (B-CLL).

A Case Description

A 71-year-old woman treated for five years at a regional outpatient clinic due to a nodular goiter was referred to the endocrinology outpatient clinic in Holy Cross Center of Oncology for a consultation and a follow-up examination.

Her physical examination and medical history revealed:
- arterial hypertension of II/III degree WHO and prolonged coronary failure;
- a pacemaker implanted 5 years earlier due to the sick sinus syndrome;
- a hysterectomy performed 30 years earlier due to myomas;
- a radioactive radium treatment at the age of 17 because of lymphadenopathy (the patient was unable to report the diagnosis made at that time owing to the lack of medical documentation).

Ultrasonography and fine-needle aspiration biopsy (FNAB) of the thyroid gland, as well as additional blood examination were performed due to the goiter enlargement, palpable surrounding lymph nodes, hoarseness, edema and compression in the neck. The size of the right lobe in the ultrasonographic examination of the thyroid was 60×21×22mm, the left lobe measured 61×27×23mm and the isthmus was ap-

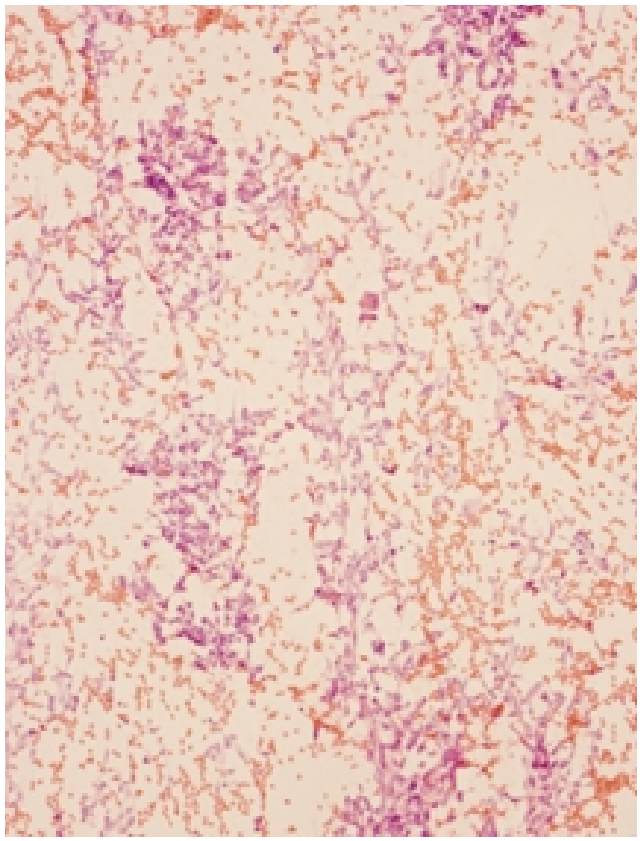

Fig. 1. FNAB – a cytological image of a medullary carcinoma.

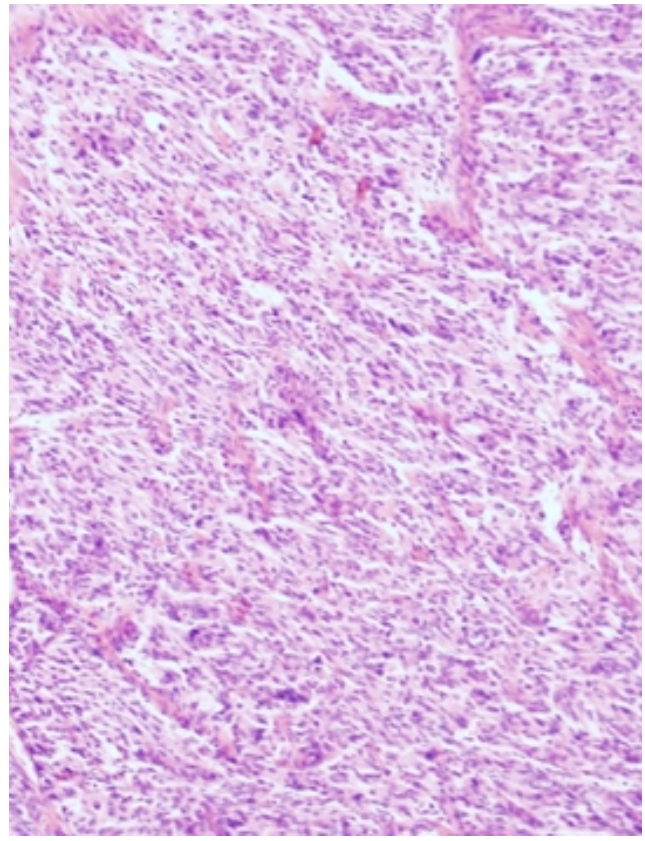

Fig. 2. A low power microphotograph of a typical area of a medullary carcinoma.

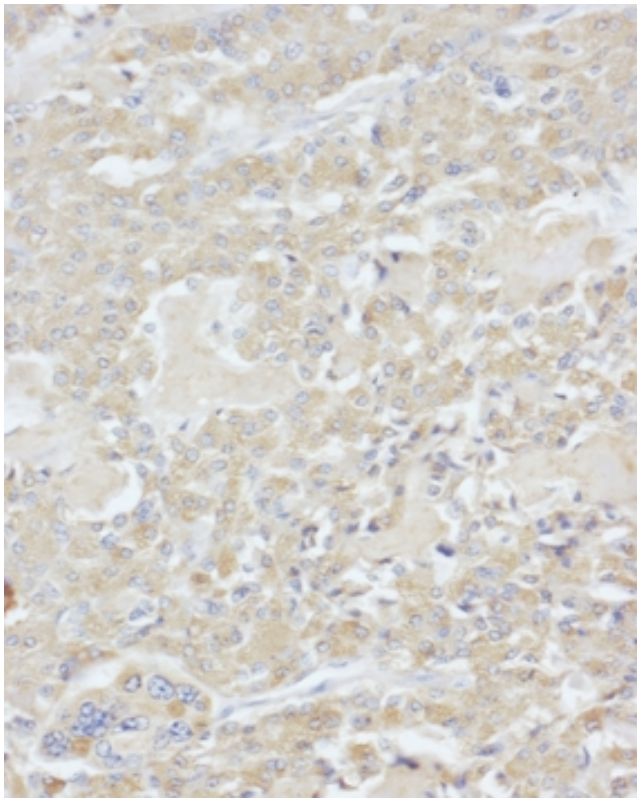

Fig. 3. Medullary carcinoma – a strong immunoreactivity for calcitonin.

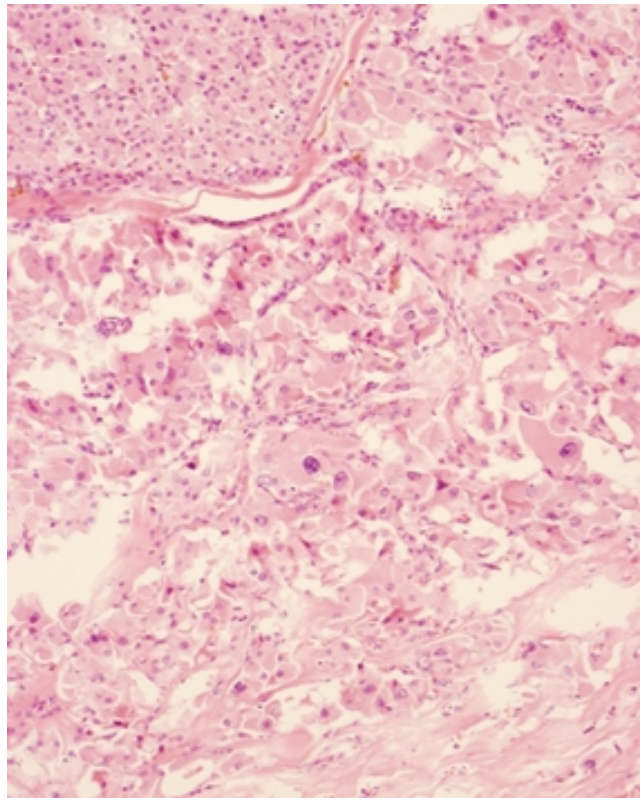

Fig. 4. A low power microphotograph of a typical area of a papillary carcinoma.

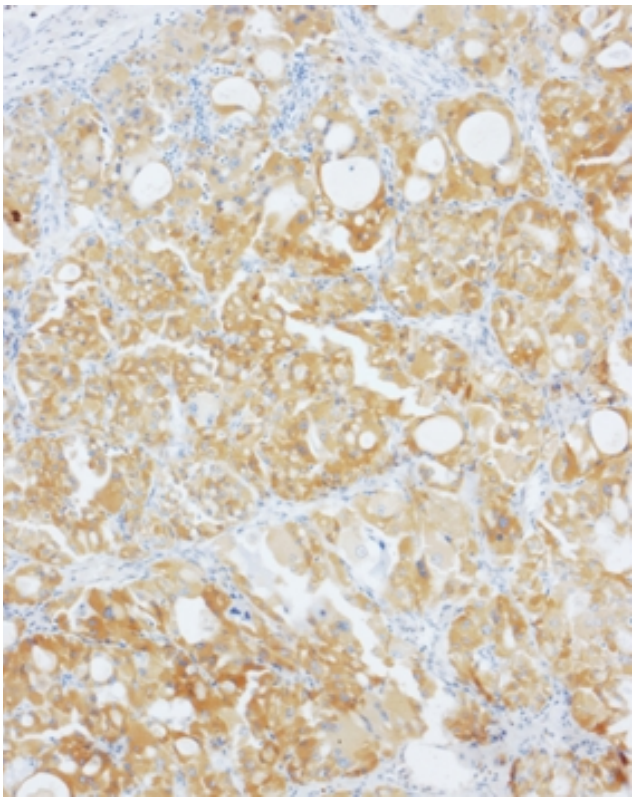

Fig. 5. Papillary carcinoma – a strong immunoreactivity for CK19.

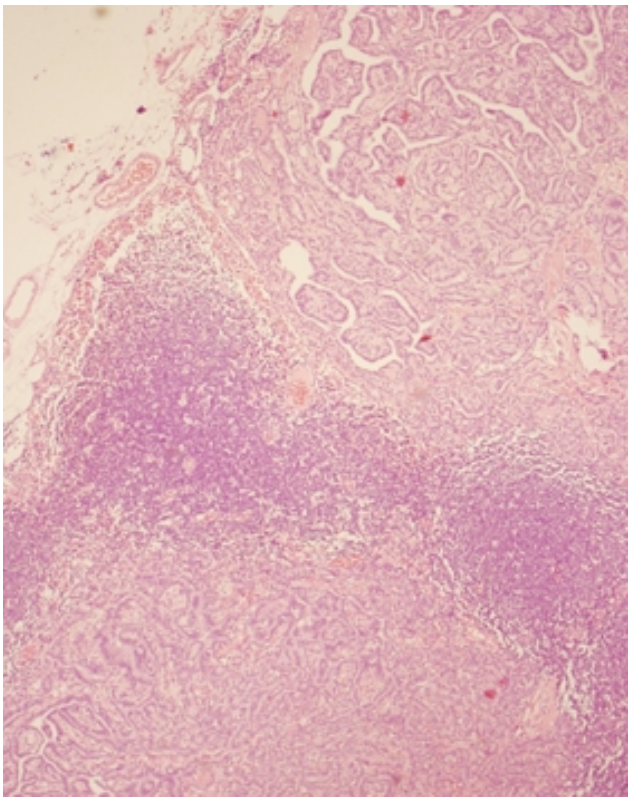

Fig. 6. A low power microphotograph of metastatic papillary carcinoma of the lymph node.

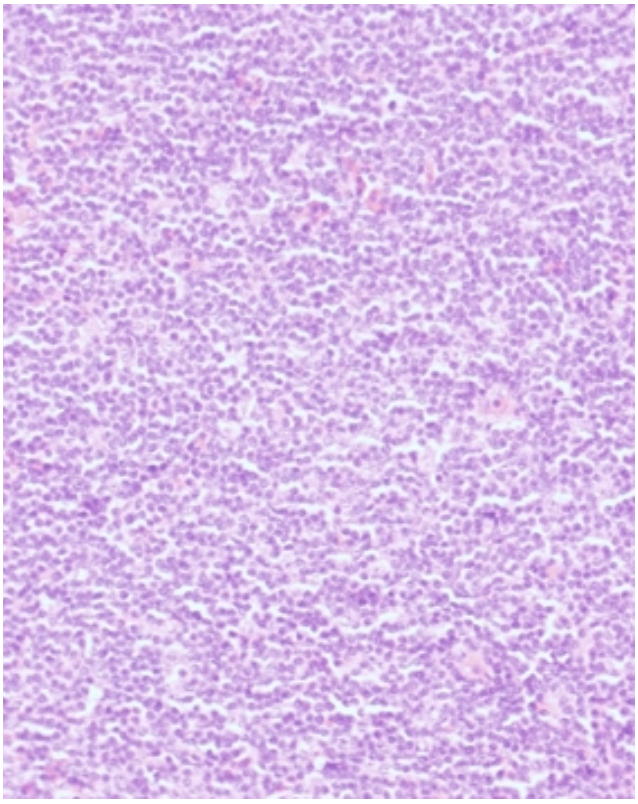

Fig. 7. A low power microphotograph of a lymph node involved by B-CLL.

proximately 5mm thick. In the left lobe, a hypoechogenic focus with calcifications measuring 30×27mm was detected; moreover, two hypoechogenic foci measuring 8×6mm and 13×8mm, respectively, were found on the border between the left lobe and the isthmus. In the right lobe, a normoechogenic focus measuring 18×16mm and hypoechogenic foci measuring 9×9mm, 11×8mm, and 11×10mm were detected. Lymph node ultrasonography demonstrated enlarged hypoechogenic axillary lymph nodes both on the right and the left side, reaching 48mm in diameter. Moreover, bilateral enlargement of hypoechogenic lymph nodes was found in the supraclavicular areas, along the sternocleidomastoid muscles and in the submandibular areas.

FNAB of the nodule in the central and inferior parts of the left lobe allowed for establishing the diagnosis of a medullary thyroid gland carcinoma (Fig. 1).

The results of the immunohistochemical examination in "cell block" tissue aspirated from the tumor were as follows: calcitonin (+), thyreoglobulin (–), chromogranin A (+). In the aspirate of the right lobe nodule, only colloidal contents were found. FNAB of the nuchal nodes ruled out carcinoma metastases. Furthermore, increased levels of CEA – 154.1ng/ml (normal range 0.0–3.0), and calcitonin >1016pg/ml (normal range <15pg/ml) were detected. The TSH level was 0.2 lU/ml (normal range 0.4–4.0 lU/ml). The calcium level

of 2.31mmol/l and the phosphorus level of 3.55mg/dl did not exceed normal values. After a surgical and cardiological consultation, the patient was qualified to a thyreoidectomy and a lateral lymphadenectomy of the neck. During the surgery, the left lobe of the thyroid was found enlarged, hard and showed profound pathological lesions. The right lobe was enlarged with numerous small nodules. Moreover, the patient presented with numerous bilaterally enlarged and suspected of metastases posterior, supraclavicular and submandibular lymph nodes.

The patient underwent a thyreoidectomy, as well as a bilateral lymphadenectomy of the neck according to the Jadwinski-Crile's procedure. After the surgery, the patient developed hypoparathyroidism and had symptoms of bilateral vocal cords paralysis with accompanying respiratory failure, which finally necessitated a tracheostomy. Nine days after the surgery, when the calcium level returned to normal, the patient was discharged.

The result of histopathological examination was as follows:

Macroscopic examination:

the right lobe 60×35×25mm in size, with a nodular surface on cross-section, with two solid nodules of 7mm and 10mm in diameter in the central part. The left lobe 50×35×25mm in size, with a solid, whitish nodule 25mm in diameter on cross-section occupying the central and inferior part of the lobe. Furthermore, 8 tissue fragments of different size with the lymph nodes were excised.

Microscopic examination:

– in the left thyroid lobe, a medullary carcinoma was detected; the tumor was 22mm in dimension (Fig. 2). The carcinoma infiltrated the thyroid capsule and was found to be in the immediate vicinity of the surgical margin. The tumor tissue was positive for calcitonin (Fig. 3) and negative for thyreoglobulin;
– in the right lobe, a bifocal papillary carcinoma was found, the encapsulated tumors were 7mm and 16mm in diameter (Figs. 4 and 5). Vascular invasion was not observed;
– in the isthmus of the thyroid, a papillary microcarcinoma was found, the tumor was 1mm in dimension and it was completely surrounded by the thyroid parenchyma;
– among the 43 dissected free left and lateral cervical lymph nodes, three were diagnosed as papillary carcinoma metastases and one was diagnosed as an extranodal metastasis (Fig. 6). In one of the lymph nodes, the carcinoma infiltrated the node capsule (the metastatic lesion was 6 mm large);
– among the three submandibular lymph nodes on the left side, one with the papillary carcinoma metastasis was detected (the metastatic lesion was 2mm large);
– in the four left supraclavicular lymph nodes, no carcinoma metastases were found;
– on the right side, in the 36 dissected free lymph nodes from the lateral cervix and submandibular region, carcinoma metastases were not detected. All the lymph nodes, both on the right and left side, were enlarged because of a small B-cell lymphoma (Fig. 7).

The results of the histopathological examination confirmed the diagnosis of a papillary carcinoma of the right thyroid lobe and isthmus with metastases to the lymph nodes, a medullary carcinoma of the left thyroid lobe and a concomitant lymphoma arising from small B cells (with a lower malignancy and a prolonged course) in all the excised nodes. The presence of lymphoma was confirmed by the immunohistochemical examination (CD5+, CD23+, Cyclin D1–).

The patient was hospitalized many times during the postoperative course at the endocrinology ward, where she underwent a postoperative radioisotope diagnostic management and was complementarily treated with radioiodine. On the 38th day after the surgery, the patient was administered 131-J at the dose of 75mCi; the treatment proceeded without any problems. In a postoperative follow-up examination, the level of CEA was 17.5ng/ml, and the level of calcitonin returned to a normal value of 5.6pg/ml.

Biochemistry showed the following test results: TSH >75 IU/ml, thyreoglobulin – 4.6ng/ml, calcium – 1.88mmol/L and phosphorus – 5.44mg/dl. Ultrasonography revealed single normal lymph nodes in both submandibular zones. A thyroxin preparation was administered in a suppressive dose and constant supplementation of calcium-phosphorus to correct metabolism disturbances.

– In the 8th month after the operation, the patient was qualified for a therapeutic dose of radioiodine – she was given 1800MBq; the treatment proceeded without any problems. In a follow-up ultrasonography of the neck, bilaterally two enlarged hypoechogenic lymph nodes were detected along the sternocleidomastoid muscles and in both submandibular zones.
– 18 months after the operation, an imaging examination revealed hypoechogenically enlarged lymph nodes in the supraclavicular zones, both axillas, mediastinum and on both sides of her neck.

The patient was tested to detect the presence of *P53* suppressor gene and *RET* proto-oncogene mutations.

DNA extraction

DNA was obtained from the studied patent specimens by the routine proteinase K digestion and phenol-chloroform extraction procedure [42]. A fresh peripheral blood

sample, as well as histological sections of formaldehyde-fixed and paraffin-embedded tissue were analyzed.

P53 mutation analysis

Mutations of *P53* gene were examined by means of the polymerase chain reaction followed by DNA direct sequencing as described previously [41].

P53 exons 5–8 were amplified individually using oligonucleotide primers and corresponding annealing temperatures as described in Table 1. After denaturing DNA at 95°C for 5min, 35 cycles of PCR (denaturation at 95°C for 1min, annealing at 58°C–61°C for 1min, and extension at 72°C for 1min) was performed in a total volume of 20 l of reaction mixture containing 50ng genomic DNA, 10 mM Tris-HCl, 50mM KCl, 1.0–1.5mM $MgCl_2$, 50 M dNTPs, 0.25 M of each *P53* fluorochrome-labeled primers and 0.5U TaqDNA polymerase (Perkin-Elmer/Cetus, CT, USA) using an automated Thermal Cycler (Perkin-Elmer 2400).

PCR fragments were purified from the gel and subjected to direct sequencing using the Sequi Therm Excel™ system (Epicentre, USA). The procedure was performed according to the Vendor's protocol. Briefly, 0.1–0.3pmol of purified DNA template, 12pmol of primer and also 1 l of Semi Therm Excel II DNA polymerase were combined with the four mixtures of all normal dNTPs and specific terminating ddNTP within, and subjected to 30s of denaturation at 95°C and 35 cycles of reaction (denaturation at 95°C for 30s, annealing at 58–61°C for 15s, and extension at 72°C for 15s). The samples were electrophoresed in an automatic DNA sequenator IR^2 LiCor through 6% polyacrylamide and 8M urea gel for 4h at 1200V, 30mA and 45°C. Final analyses were performed with the Align software.

RET mutation analysis

Mutations of the *RET* gene were tested by means of the polymerase chain reaction followed by PCR-RFLP analysis and direct DNA sequencing [21, 40].

RET exons 10, 11 and 16 were amplified individually using oligonucleotide primers and corresponding annealing temperatures as described in Table 2. After denaturing DNA at 95°C for 5min, 35 cycles of PCR (denaturation at 95°C for 1min, annealing at 58–68°C for 1min, and extension at 72°C for 1min) were performed in a total volume of 20 l of reaction mixture containing 50ng genomic DNA, 10mM Tris-HCl, 50mM KCl, 1.5–2.5mM $MgCl_2$, 50 M dNTPs, 0.25 M of each *RET* fluorochrome-labeled primers and 0.5U Taq DNA polymerase (Perkin-Elmer/Cetus, CT, USA) using an automated Thermal Cycler (Perkin-Elmer 2400).

Point mutations of the *RET* gene in the codon 634 (exon 11) and codon 918 (exon 16) were detected by the specific PCR-RFLP method. To receive a proper amount of the amplified material for RFLP assays, the polymerase chain reactions were performed in final 100 l volume. In brief, 155bp long PCR product of the amplified exon 11 DNA was cut with *CfoI, RsaI, DdeI, ItaI and HaeIII* restriction nucleases at 37°C for 3–12 hours, and 192bp long PCR product of the amplified exon 16 DNA was digested with *FokI* restrictase. The products of all treated DNA

TABLE 1

The nucleotide sequences of oligonucleotide primers used for *P53* gene amplification

Exon	Primer sequence	Annealing temperature	Size of PCR product
5	5'-TTCCACACCCCCGCCCGGCA-3' 5'-ACCCTGGGCAACCAGCCCTG-3'	60°C	178 bp
6	5'-ACAGGGCTGGTTGCCCAGGG-3' 5'-AGTTGCAAACCAGACCTCAG-3'	58°C	213 bp
7	5'-ACTGGCCTCATCTTGGGCCT-3' 5'-GTCAGAGGCAAGCAGAGGCT-3'	60°C	208 bp
8	5'-TAAATGGGACAGGTAGGACC-3' 5'-TCCACCGCTTCTTGTCCTGC-3'	61°C	227 bp

TABLE 2

The nucleotide sequences of oligonucleotide primers and parameters used for RET gene amplification

Exon	Primer sequence	Annealing temperature	Mg^{2+} (mM)	Size of PCR product
10	5'-CTCAGGGGGCAGCATTGTT -3' 5'-CACTCACCCTGGATGTCTT -3'	58°C	1.5	132 bp
11	5'-CCTCTGCGGTGCCAAGCCTC -3' 5'-TGTGGGCAAACTTGTGGTAGCA -3'	68°C	2.5	155 bp
16	5'-AGGGATAGGGCCTGGGCTT -3' 5'-TAACCTCCACCCCAAGAG -3'	60°C	1.5	192 bp

specimens were electrophoresed using 3% agarose gel. In the case of mutated codon 634, different transition or transversion changes create restriction sites for particular nucleases and specific digestion fragments can be observed in the gels. Contrary to that, the samples with only "wild-type" codon 918 were cleft by *FokI*, giving two fragments as a result. The point mutation at this codon removed a *Fok I* restriction site.

Screening for mutation in exon 10 was performed with the DNA direct sequencing test (as described above for *P53* gene mutation).

Results

No germline mutations in *P53* and *RET* genes of DNA isolated from the peripheral blood sample were observed. This finding excluded the Li-Fraumeni and MEN 2 syndromes as an explanation of the diagnosed multiple tumors. But other specific genetic changes, common for all three tumors, may exist, and thus further studies are necessary. The lack of alterations of both genes in the studied specimens indicated that other particular molecular pathways were responsible for malignant cell transformations.

Discussion

A simultaneous occurrence of a medullary and papillary carcinoma in the same thyroid gland and a metastasis to lymph node is extremely rare [14, 24, 43, 44].

In some of the reported cases, one type of tumor was identifiable at the light microscopic level, and the other type of carcinoma was diagnosed by immunohistochemical and structural studies [10, 13, 28, 35]. In other cases, it was possible to diagnose histologically the medullary and follicular components [3]. The former type is regarded as a mixed tumor and the latter as a composite tumor.

Papillary carcinoma is the most common type of thyroid malignancy and comprises approximately 80% of all thyroid malignancies [26]. Multiple microscopic foci of papillary thyroid carcinoma are found in about 20% of the thyroid carcinoma cases if a few random sections are taken, and in over 75% if step sections of the entire gland are examined [5, 19, 22, 34]. A controversy still exists regarding whether this represents multicentricity [23] or an intrathyroidal lymphatic spread [27].

Medullary carcinoma of the thyroid was first described by Hazard at al. [46]. They emphasized its non-follicular and solid growth pattern. Medullary carcinoma of the thyroid may often show unusual histological features, such as follicles, papillae, trabeculae, oxyphilic and small cells, and even squamous or anaplastic features, which may mimic other tumors and pose problems in histological interpretation [46]. Fortunately, immunohistochemical studies usually confirm the parafollicular origin (C-cells) of the tumor – neoplastic cells with follicular and papillary structures are positive for calcitonin and not thyreoglobulin [31]. Interestingly, sometimes there is a C-cell hyperplasia in tissues adjacent to non-medullary carcinomas of the thyroid [2]. In these cases, the primary tumors do not stain positive for calcitonin.

Medullary carcinoma of the thyroid, which produces calcitonin and other hormonal peptides, is generally considered to arise from the parafollicular cells (C-cells) of the ultimobranchial body derived from the fourth pharyngeal pouch. On the other hand, differentiated carcinomas, papillary and follicular carcinoma of the thyroid, which produce thyreoglobulin and thyroid hormones, are thought to originate from the follicular epithelial cells derived from a median endodermal anlage from the tongue. Thus, it is generally believed that the origin of each carcinoma is embryologically different. Therefore, it is of interest to note this coincidence of medullary carcinoma and papillary carcinoma of the thyroid in the same thyroid gland. Thus, there is a possibility that an occult papillary carcinoma may be found within a thyroid gland with a concomitant medullary carcinoma [33]. Interestingly, some cases of thyroid carcinoma with a mixed medullary and follicular pattern have been reported in the literature [6, 10, 13, 17, 28, 35, 36, 38, 39, 47]. Many investigators suggested one possibility regarding the histogenesis of a mixed medullary and follicular carcinoma of the thyroid. It could be derived from neoplastically transformed uncommitted stem cells with the capacity to differentiate into tumor components with morphological and histochemical characteristics of both follicular and medullary neoplasms. Kameda et al. believed that not only C-cells, but also follicular epithelial cells appeared to be derived from the ultimobranchial body in dog thyroid [15, 16]. A couple of studies have provided evidence that some C-cells and follicular epithelial cells are derived from the human ultimobranchial body [11, 49].

This would be conflicting with the current opinions. Volante et al. [48] demonstrated that the follicular and medullary components in mixed medullary and follicular carcinoma were not derived from a single progenitor cell, because they observed different patterns of RET proto-oncogene mutation, LOH, and X-chromosomal inactivation (clonality). According to Matias-Guiu, the confirmation of so called "hostage hypothesis" would require the unknown trophic factors, which are necessary for the stimulation of follicular cells, as well as the detection of these substances in the medullary thyroid cells of mixed medullary and follicular carcinomas and their absence in classical medullary thyroid cells.

A more plausible theory is a common tumorigenic stimulus triggering neoplastic transformation of both parafollicular C-cells and follicular epithelial cells. Prior radiation [45] or UV exposure [8] have been claimed to induce cell growth and neoplasia in both types of cells.

Interestingly, there was a history of prior radiation in our patient. The patient reported a history of lymphadenopathy in the 60s. The pathologic effects of ionizing radiation have long been known.

The patient described by us suffers from a B-CLL lymphoma, but it is hard to comment on the clinical significance of her prior radiation history. Low doses of radiation do not appear to be associated with non-Hodgkin's lymphoma (NHL), although NHL does arise infrequently following high-lethal, radiation treatments [4].

There is also a well-known genetic predisposition to thyroid cancers. They may or may not be a part of MEN and occur in a familial form [18]. Medullary carcinoma may be a prominent component of MEN II. A missense mutation in exon 10 and 11 of the *RET* proto-oncogene is associated with MEN IIA [7]. Our patient did not have a positive *RET* mutation. It has been reported that the *PTC* oncogene and somatic rearrangements of *RET* may occur in both naturally occurring and radiation-induced human papillary carcinoma of the thyroid [7, 9]. We could not perform a *PTC* analysis on the specimen due to technical difficulties.

In our case, the medullary and papillary carcinoma of the thyroid existed not only in the remnant thyroid gland, but also as the metastasis in a lymph node with B-CLL. The lack of *P53* gene germline mutation excluded the existence of the Li-Fraumeni syndrome. Immunoreactivity to calcitonin, CEA, and thyreoglobulin made a sharp distinction between the two tumors. It seems reasonable that the concurrence of a medullary carcinoma and papillary carcinoma of the thyroid in this case was probably a reflection of a true composite tumor and in this case did not have embryological or genetic significance.

Acknowledgements: The authors would like to thank Professor R. Maryniak from the Institute of Hematology and Blood Transfusion, Warsaw, Poland, for the evaluation and consultation of slides.

References

1. *Albores-Saavedra J, Gorraez de la Mora T, De la Torr-Rendon F, Gouid E:* Mixed medullary-papillary carcinoma of the thyroid: a previous unrecognized variant of thyroid carcinoma. Hum Pathol 1990, 21, 1151–1155.
2. *Albores-Saavedra J, Monforte H, Nadji M et al:* C-cell hyperplasia in thyroid tissue adjacent to follicular cell tumor. Hum Pathol 1988, 19, 795–799.
3. *Apel RL, Alpert LC, Rizzo A, LiVolsi VA, Asa SL:* A metastasizing composite carcinoma of the thyroid with distinct medullary and papillary components. Arch Pathol Lab Med 1994, 118, 1143–1147.
4. *Boice JD:* Radiation and non-Hodgkin's lymphoma. Cancer Res 1992, 52(suppl), 5489–5491.
5. *Bondeson L, Ljundberg O:* Occult papillary thyroid carcinoma in the young and the aged. Cancer 1984, 53, 1790–1792.
6. *Bussolati G, Monga G:* Medullary carcinoma of the thyroid with atypical patterns. Cancer 1979, 44, 1769–1777.
7. *Fusco A, Grieco M, Santoro M et al:* A new oncogene in human thyroid papillary carcinoma and their lymph nodal metastasis. Nature 1987, 328, 170–172.
8. *Goncales-Octobar R:* Concurrence of a symptomatic encapsulated follicular carcinoma, an occult papillary carcinoma and a medullary carcinoma in the same patient. Histopathology 1992, 21, 380–382.
9. *Grieco M, Santoro M, Berlingeri MT et al:* PTC is a novel rearranged from the RET protooncogene and is frequently detected *in vivo* in human thyroid carcinomas. Cell 1990, 60, 557-563.
10. *Hales M, Rosenau W, Okerlund MD et al:* Carcinoma of the thyroid with a mixed medullary and follicular pattern: Morphologic, immunohistochemical and clinical laboratory studies. Cancer 1982, 50, 1352–1359.
11. *Harach HR:* Thyreoglobulin in human thyroid follicles with acid mucin. J Pathol 1991, 164, 261–263.
12. *Hazard JB, Hark WA, Crile C:* Medullary (solid) carcinoma of the thyroid. A clinicopathologic entity. J Clin Endocrinol 1959, 19, 152–161.
13. *Holm R, Sobrino-Simoes M, Nesland JM et al:* Medullary thyroid carcinoma with thyreoglobulin immunoreactivity: A special entity? Lab Invest 1987, 57, 258–268.
14. *Ishida T, Kawai T, Iino Y et al:* Concurrent medullary carcinoma adjacent to papillary carcinoma of the thyroid: A clinicopathological and electron microscopic study. Gan No Rinsho 1985, 31, 1814–1820.
15. *Kameda Y, Shigemoto H, Ikeda A:* Development and cytodifferentiation of C-cell complexes in dog fetal thyroids: An immunohistochemical study using anti-calcitonin, anti-C-thyreoglobulin and anti-19S thyreoglobulin antisera. Cell Tissue Res 1980, 206, 403–415.
16. *Kameda Y, Ikeda A:* Immunohistochemical reactions of C-cell complexes in dog after hypercalcemia, antithyroid drug treatment and hypophysectomy. Cell Tissue Res 1980, 208, 417–432.
17. *Kashima K, Yokoyama S, Inoue S et al:* Mixed medullary and follicular carcinoma of the thyroid: Report of two cases with an immunohistochemical study. Acta Pathol Jpn 1993, 43, 428–433.
18. *Katagiri M, Ohtawa T, Ito K, Harada T*: Familial non-multiple endocrine neoplasia medullary thyroid carcinoma: report of a case confirming a new clinical entity in Japan. Surg Today 1995, 25, 822–826.
19. *Katoh R, Sasaki J, Kurihara H, Suzuki K, Iida Y, Kawaoi A:* Multiple thyroid involvement (intraglandular metastasis) in papillary thyroid carcinoma. A clinicopathologic study of 105 consecutive patients. Cancer 1992, 70, 1585–1590.
20. *Kobayashi K, Teramoto S, Maeta H, Ishiguro S, Mori T, Horie Y:* Simultaneous occurrence of medullary carcinoma and papillary carcinoma of the thyroid. J Surg Oncol 1995, 59, 276–279.
21. *Komminoth P, Kunz EK, Matias-Guiu X, Hirot O, Christiansen G, Colomer A, Roth J, Heitz PU:* Analysis of *RET* protooncogene point mutations distinguishes heritable from nonheritable medullary thyroid carcinomas. Cancer 1995, 76, 479–489.
22. *Komorowski RA, Hanson GA:* Occult thyroid pathology in the young adult: an autopsy study of 138 patients without clinical thyroid disease. Hum Pathol 1988, 19, 689–696.
23. *Kosem M, Kotan C, Algun E, Topal C:* Simultaneous occurrence of papillary intrafollicular and microcarcinomas with bilateral medullary

microcarcinoma of the thyroid in patient with multiple endocrine neoplasia 2A:report of a case. Surg Today 2002, 32, 623–628.
24. *Lamberg BA, Stenman RS, Koivuniemi A et al:* Concurrent medullary and papillary thyroid carcinoma in the same thyroid lobe and in siblings Acta Med Scand 1981, 209, 421–424.
25. *Lax SF, Beham A, Kronberger SD, Langsteger W, Denk H:* Coexistence of papillary and medullary carcinoma of the thyroid gland – mixed or collision tumour? Clinicopathological analysis of three cases. Virchows Arch 1994, 424, 441–447.
26. *LiVolsi VA:* The thyroid and parathyroid. In: Diagnostic Surgical Pathology. Sternberg SS, ed. 2nd ed. New York:Raven 1994, 523–560.
27. *LiVolsi VA:* Surgical Patology of the Thyroid. 1st ed. W.B. Saunders Company 1990, 136–166.
28. *Ljunberg O, Ericsson UB, Bondeson L et al:* A compound follicular-parafollicular cell carcinoma of the thyroid: A new entity? Cancer 1983, 52, 1053–1061.
29. *Lyss AP, Thompson JJ, Glict JH:* Adenocarcinoid tumor of the colon arising in preexisting ulcerative colitis. Cancer 1981, 48, 833–839.
30. *Macak J, Vaverkova H, Dushova M, Perlerorova I:* Medullary and medullary-papillary carcinoma of the thyroid gland. Pathologica 1997, 89, 317–322.
31. *Matias-Guiu X, Caixas A, Costa L, Cabezas R, Prat J:* Compound medullary-papillary carcinoma of the thyroid: true mixed tumour. Histopathology 1994, 25, 183–185.
32. *Michal M, Curic R, Macak J, Ludvikova M, Dedic K:* Mixed medullary-follicular and medullary-papillary carcinoma of the thyroid: one or two entities? Zentralbl Pathol 1993, 139, 333–335.
33. *Miyauchi A:* Clinicopathologic and endocrinological studies on 33 cases of medullary carcinoma of the thyroid. Part 2. Jpn J Surg Soc 1978, 79, 271–284.
34. *Nasir A, Chaudhry AZ, Gillespie J, Kaiser HE:* Papillary microcarcinoma of the thyroid: a clinico-pathologic and prognostic review. In Vivo 2000, 14, 367–376.
35. *Ogawa H, Kino I, Arai T:* Mixed medullary-follicular carcinoma of the thyroid. Immunohistochemical and electron microscopic studies. Acta Pathol Jpn 1989, 39, 67–72.
36. *Parker LN, Kollin J, Wu SY et al:* Carcinoma of the thyroid with a mixed medullary, papillary, follicular and undifferentiated pattern. Arch Intern Med 1985, 145, 1507–1509.
37. *Pastolero GC, Coire CI, Asa SL:* Concurrent medullary and papillary carcinomas of the thyroid with lymph node metastases. A collision phenomenon. Am J Surg Pathol 1996, 20, 245–250.
38. *Perrone T:* Mixed medullary-follicular thyroid carcinoma. Am J Surg Pathol 1986, 10, 362–363.
39. *Platz M, Hedinger CE, Muehlethaler JP:* Mixed medullary and follicular carcinoma of the thyroid. Virchow Arch A 1983, 400, 53–59.
40. *Pomorski L, Bartkowiak J, Pisarek H, Bartos M, Narębski J:* Medullary thyroid carcinoma (MTC) – clinical and molecular aspects on the basis of own experience. Neoplasma 2000, 47, 323–326.
41. *Rieske P, Bartkowiak J Szadowska A, Olborski B, Harezga-Bal B, Debiec-Rychter M:* A comparative study of *P53*/MDM2 genes alternations and P53/MDM2 proteins immunoreactivity in soft-tissue sarcomas. J Exp Clin Cancer Res 1999, 18, 403–416.
42. *Sambrook J, Fritsch EF, Maniatis T:* Molecular Cloning. A Laboratory Manual. 2nded. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York 1989.
43. *Suzumura K, Koike Y, Naruse T et al:* Coincidence of medullary and papillary carcinomas of the thyroid. A case report. Endocrinol Surg 1991, 10, 147–151.
44. *Taniguchi M, Koike Y, Nogushi S et al:* A case of concurrent medullary and follicular thyroid carcinoma. Endocr Surg 1993, 10, 147–151.
45. *Triggs SM, Williams ED:* Experimental carcinogenesis in the rat thyroid follicular and C cells. Acta Endocrinol 1977, 85, 84–92.
46. *Uribe M, Grimes M, Fenoglio-Preiser C, Feind C:* Medullary carcinoma of the thyroid gland. Am J Surg Pathol 1985, 9, 577–594.
47. *Valenta LJ, Michel-Bechet M, Mattson JC, Singer FR:* Microfollicular thyroid carcinoma with amyloid rich stroma, resembling the medullary carcinoma of the thyroid (MCT). Cancer 1977, 39, 1573–1586.
48. *Volante M, Papotti M, Roth J, Saremaslani P, Speel EJM, Lloyd RV, Carnei AJ, Heitz PhU, Bussolati G, Komminoth P:* Mixed medullary-follicular thyroid carcinoma: molecular evidence for a dual origin of tumor components. Am J Pathol 1999, 155, 1499–1509.
49. *Williams ED, Toyn CE, Harach HR:* Ultimobranchial body and congenital abnormality in man. J Pathol 1989, 159, 135–141.

Address for correspondence and reprint requests to:
Dr A. Bocian
Department of Surgery
Holycross Cancer Center
Artwińskiego 3, 25-734 Kielce
tel.: 601-924-611
e-mail: abocian@mp.pl