

Quadruple Metachronous Malignancy in a Single Patient with Multiple Sclerosis

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ABSTRACT

Quadruple primary malignancies occur with an incidence of less than 0.1%. Only less than hundred cases have been published until today. The number of multiple malignancies reported is gradually increasing. Here, we present a female patient with a multiple sclerosis and quadruple cancers from different embryological origin. The patient had medullary thyroid carcinoma (stage III-T3, N1a, M0) and multicentric micropapillary carcinomas, two melanomatous lesions, 1.24 and 0.85 mm thick (Clark II, Breslow II) and breast cancer (T1a, N0, M0). There were no signs of disease recurrence during the 5 years including the exam performed last month. Further genomic studies and closer clinical attention are needed to clarify the relation between secondary malignancies, applied treatments and endogenous and exogenous carcinogens in the process of carcinogenesis in quadruple malignancies.

Keywords: Quadruple malignancy, Multiple sclerosis, Carcinogenesis.

How to cite this article: Buta M, Ito Y, Radisavljevic Z, Milovanovic Z, Lavrnica D, Djurisc I, Oruci M, Pupic G, Dzodic R. Quadruple Metachronous Malignancy in a Single Patient with Multiple Sclerosis. *World J Endoc Surg* 2012;4(2):79-82.

Source of support: Nil

Conflict of interest: None declared

INTRODUCTION

Multiple primary malignancies are two or more malignancies in an individual without any relationship between the tumors.¹ Multiple malignancies in a single patient are rare but have increased in frequency in recent years.² Multiple primary cancers occurs in 3 to 5% of malignant tumors and they are frequent in the head and neck, triple tumors occur in only 0.5%, but quadruple tumors in 0.1 to 0.3%.^{3,4} Quadruple primary malignancies were found in less than hundred cases during the past three decades.⁵ Quadruple cancer, including triple cancers in the head and neck region, was reported.⁴ Quadruple lung cancer in single patient has also been reported⁶ as well as quadruple primary malignancies of the liver, bladder, lung and stomach, all which have been linked to the p53 mutation.¹ There are similar case reports in the literature describing various combinations of quadruple malignancies affecting almost all organs.⁷⁻⁹ We present a case of multiple sclerosis with two different thyroid carcinomas, melanoma and breast cancer.

CASE REPORT

A 40-year-old woman was diagnosed with multiple sclerosis in 1994 and because of the severe relapsing-remitting course of the disease she was treated with pulsative steroid therapy and short time with azathioprine. Seven years later disease become secondary progressive when patient was treated with mitoxanthrone (8 mg/m² intravenously every 3 months, for 15 months). There were no drug-related serious adverse events or evidence of clinically significant cardiac dysfunction. This therapy abolished the progression of disease. The patient had only moderate spastic paraparesis with gait difficulties. Expanded disability status scale (EDDS) at that time was 5. In family history patient's father had thyroid carcinoma, grandmother had gastric cancer and uncle had pancreatic carcinoma.

In the year 2007, 4 years after discontinuation of mitoxanthrone therapy, at the age of 53, patient presented with a cold thyroid, hypoechoic nodule in the right thyroid lobe 42 mm in diameter and a node of 3.3 mm in the left lobe. Serum calcitonin value was elevated over 2000 ng/l. The patient underwent total thyroidectomy, central node dissection (pretracheal and paratracheal bilateral) and sentinel lymph node biopsy of both jugular chains. Patient had stage III (T3, N1a, M0) medullary thyroid carcinoma size 45 mm in the right lobe (calcitonin +, Tg ±, CEA +, synaptophysin +, NSE +, chromagranin +, bcl2 +) (Fig. 1) and two micropapillary carcinomas in the left lobe,

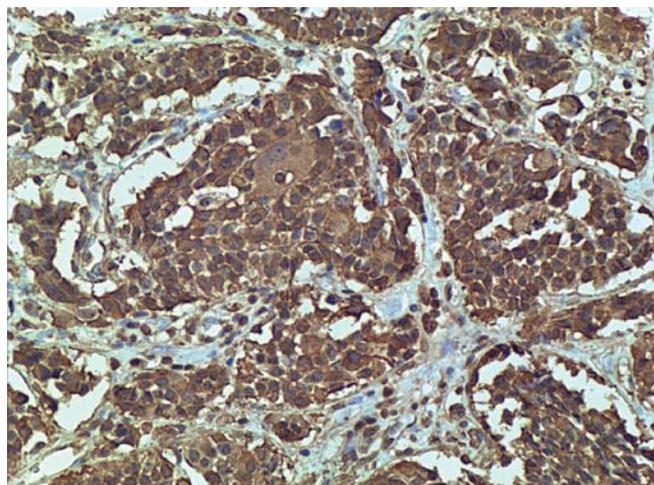


Fig. 1: Medullary thyroid carcinoma anticalcitonin antibody staining of medullary thyroid carcinoma H and E x10

size 1.5 and 0.5 mm, medullary thyroid carcinoma metastases in the central neck region (4/12) with negative sentinels bilaterally (0/6 in the left jugular chain and 0/2 in the right jugular chain). Postoperative calcitonin value was 81,7 pg/l, CEA 2.75 ng/l and whole body scan after 24 hours showed 0.93% fixation over the central neck region and no fixation over the thorax. Multidisciplinary committee decided a patient should be treated with external 60 Gy beam irradiation of neck and mediastinum and L-thyroxine suppression therapy.

A year later of the thyroid surgery, in the year 2008, patient complained on enlargement of pigmented skin lesion located over right scapula and other pigmented skin lesion was discovered during the clinical examination in the left lumbar region. Preoperative scintigraphy was performed and one hot node was identified in the right axilla. Both skin tumors were radically excised with more than 10 mm margins and histopathology revealed 1, 24 mm thick scapular melanoma-superficial spreading type (Clark II, Breslow II) and 0.85 mm thick lumbar melanoma-superficial spreading type (Clark II, Breslow II) (Fig. 2) with negative axillary sentinel node.

Fourteen months later, while the perimenopausal patient was on regular follow-up, the breast tumor was discovered on mammography as a stellate lesion 10.8 × 6.3 mm, BIRADS 5, for which she underwent quadrantectomy with level I and partially level II axillary lymph nodes dissection. Histopathology showed lobular invasive 4 mm breast carcinoma with LCIS and DCIS (lobular and ductal carcinoma *in situ*) (HG II, NG II, CK7+, LCA-) (Fig. 3), clear resection margins and negative nodes (0/1). An estrogen and progesterone receptors were strongly positive and human epidermal growth factor receptor-2 overexpression was minimal. Patient underwent 40 Gy postoperative radiotherapy of the left breast (extended field)

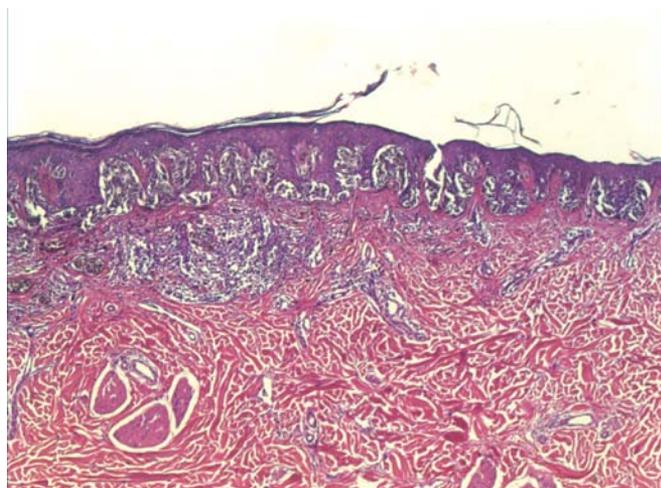


Fig. 2: Skin melanoma invasive cutaneous melanoma H and E ×10

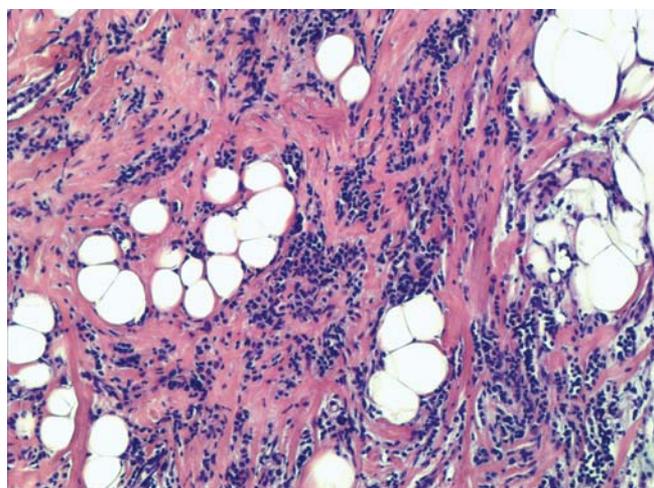


Fig. 3: Breast cancer invasive lobular breast cancer H and E ×10

considering the fact that she had been previously treated with 60 Gy in the neck and mediastinum due to thyroid carcinoma. During the course of her treatment, patient became postmenopausal and 20 mg tamoxifen daily was added to her treatment.

Patient is on regular follow-up without signs of recurrence. FDG-PET scan performed in December 2011 was negative, CA 15-3 level was within normal limits and calcitonin level was 83 ng/l and CEA 5 ng/l. Brain MRI indicated multiple foci of demyelination, without active lesions, and in comparison with the previous MRI findings there were no signs of the disease progression. Also, neurological examination performed in December 2011 did not show any signs of disease progression. She had moderate spastic paraparesis, and EDSS still 5, as it was 4 years ago.

DISCUSSION

We report a case of quadruple nonsynchronous malignancy in a single patient with multiple sclerosis where cancers are from different embryological origin. Quadruple malignancy is a rare phenomenon in medicine and most cases of multiple malignancies affect one organ in a female patient. From 1980 to 2011, only 89 cases of primary quadruple malignancy have been reported.⁵ It would be easier to explain multiple carcinomas of same or similar histological origin than tumors originating from different embryological tissues as in our case (melanocytes from neuroectoderm, breast from ectoderm, thyroid gland from endoderm, C cells from neural crest).¹⁰ There are many possible causes of multiple malignancies, such as genetic mutation and family history, exposure to anticancer chemotherapy, radiotherapy, reduced immunologic response and smoking. Multiple malignancies could be in some instances linked to Li Fraumeni and Lynch syndrome but such an association

could not be established in our case. Our patient had family history of malignancy on mother's and father's side (father, grandmother and uncle). Patient has not received chemotherapy with alkylating agents which are well known cause of secondary cancers. The patient received mitoxanthrone, a drug extensively used as a disease-modifying therapy for multiple sclerosis. However, this treatment could be linked to nonmelanocytic skin tumors and increased susceptibility to develop acute promyelocytic leukemia.¹¹⁻¹³ A high incidence of synchronous or metachronous breast cancer has been reported in patients with malignant thyroid tumor.¹⁴ The patient was treated with total thyroidectomy, central neck dissection and sentinel lymph node biopsy of both jugular chains. Sentinels were negative bilaterally and prophylactic modified radical neck dissection has not been performed.¹⁵ The patient was treated postoperatively with 60 Gy external beam radiotherapy (EBRT) of neck and mediastinum but that could not explain development of later breast cancer and melanoma considering short time from exposure to the development of carcinoma.

It is very likely that some genetic alterations were involved in the development of quadruple cancer but genetic testing has not been done yet. The number of multiple malignancies reports is slowly but gradually increasing.⁷ A familial cancers study provided answers and discovery of germ-line mutations of genes during tumorigenesis through loss of heterozygosity (LOH) resulting from somatic deletions or recombinations.¹⁶ LOH allowed cloning of RB gene¹⁷ and identify the genes that are responsible for familial colon and breast cancers.¹⁸⁻²⁰

Epidemiological study have shown an increased incidence of malignancies in patients with multiple sclerosis (MS).²¹ Genetic alterations may affect tumor suppressor genes important in carcinogenesis of quadruple cancers.¹⁶ RB (retinoblastoma), a tumor-suppressor gene which inhibits cell-cycle progression at the G1/S checkpoint is very important as trigger for cancer proliferation. Rb responds to external growth-factor stimulation by becoming phosphorylated at specific sites, which, in turn, removes the inhibitory influence and allows passage through the checkpoint allowing cancer cell fast proliferation.¹⁶ FOXO3A gene play important role in development of cancers through the signaling pathway regulating apoptosis NOS/ROCK/FOXO3A.²² Cancer growth is supported by the angiogenesis pathay VEGF/PI3K/AKT/NOS/ICAM1 where ICAM-1 is effector protein.²³ Development of quadruple cancers got extreme robustness by formatting positive loop systems allowing generations of cancer robustness and progression.^{24,25}

ABBREVIATIONS

AKT: Serine/threonine protein kinase (PKB, protein kinase B); LCIS and DCIS: Lobular and ductal carcinoma *in situ*; EDDS: Expanded disability status scale; FOXO3A: Forkhead box group O; ICAM-1: Intracellular adhesion molecule 1; LOH: Loss of heterozygosity; MS: Multiple sclerosis; NOS: Nitric oxide synthase; PI3K: Phosphoinositol-3-OH kinase; RB (retinoblastoma); mTOR: Mammalian target of rapamycin; VEGF: Vascular endothelial growth factor.

ACKNOWLEDGMENT

This study was supported by Grant III41031 from the Ministry of Education and Science, Republic of Serbia.

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