

ABCB5 in peripheral blood of a patient affected by multiple primary malignancies



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BACKGROUND: Multiple primary neoplasm malignancies syndrome (MPMN), is the presence of two or more abnormal growths of tissue, occurring simultaneously. Although the number of second malignancies is increasing, due to several factors, the presence of triple or quadruple malignancies is still very rare.

PATIENT AND METHODS: We report a case of a 78-year-old man, with six primaries: a prostatic adenocarcinoma, breast cancer, two melanoma, a basal cell carcinoma, and a lymphoma in a four years period.

RESULTS: The onset of MPMN is probably caused by a mutation of DNA repair genes, probably the TP53 gene. Common features of this syndrome are early rise and low tendency to metastatize. We reviewed the markers of staminality for various tumors: RNA expression of ALDH1, CD 133, and ABCB 5, extracted from the sentinel lymph node (SLN) and from the peripheral blood of the patient, was verified.

CONCLUSION: People with multiple tumors represent a segment of the cancer-survivor population, which is continuously increasing (10%). Several genetic mutation can be involved in this kind of population. Our patient was positive for the expression of ABCB5, a marker for staminality of melanoma, in periphph blood.

KEY WORDS: Breast cancer; Melanoma Multiple primary neoplasms.

Introduction

Multiple primary neoplasm malignancies syndrome (MPMN), is defined as the presence of two or more abnormal growths of tissue, occurring simultaneously, and presumed to be of separate origin. The neoplasm may be histologically the same or different, and may be found in same or different sites. The term, multiple primary neoplasms was first described by Billroth, in 1889 ¹. The occurrence of MPMN in a patient's lifetime is not so

uncommon. Due to the growing number of cancer survivors, there is a consistent possibility of a second primary. The Italian cancer registries reported a range of 2.1% to 6.6% people affected by MPMN of all cases between 1935 and 1995 ²⁻⁵. Furthermore, this number is increasing; reaching 16% of all cases in 2003.⁶ American estimates the incidence of MPMN, between 1975 and 2001, as 756, 467 people diagnosed with more than one primary cancer. This prevalence is about 8% of all tumors, similar to the Italian data. Caucasian women experience the highest rate of both multiple tumors, and single tumors. Breast, colon and rectum, and prostate are the sites with the highest prevalence of multiple tumors ⁷. Although the number of multiple primary increased, the evidence of triple or quadruple malignancies is still very rare. In this report, we describe the case of a 78-year-old Caucasian man affected by six multiple primary malignancies.

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Case experience

In September 2007, a 78-year-old Caucasian man was admitted to the Department of Dermatology and Plastic Surgery at "Sapienza" University of Rome, with a pigmented lesion of 2 x 1 cm on the left preauricular region. The clinical history of the patient started in 2005, when he underwent a radical mastectomy of the left breast with axillary nodes dissection for a infiltrating ductal carcinoma of 2.6 cm of diameter (**first primary**). This kind of neoplasia is considered quite rare in males (0.6% of all breast tumors)⁸. The histological analysis of nodes found no presence of metastasis from the breast cancer, but showed another primary. Fifteen nodes were positive for spread B cell (CD 20+, CD79+) lymphoma (**second primary**). In June 2007, the patient underwent a radical prostatectomy after a biopsy showed the presence of a differentiated adenocarcinoma (Gleason 5) (**third primary**). In July 2007, the patient underwent an excision of a pigmented lesion that appeared on the back, with a histological analysis consistent of a melanoma (**fourth primary**). Melanoma was IV on the Clark scale, and 2.35 mm thick (Breslow). The lesion was close to the left axilla, so a sentinel lymph node dissection was not performed. In September 2007, the patient was subjected to an enlargement of the previous wound, while at the same time a lesion of the preauricular region was ablated. Histological analysis of the last lesion documented another melanoma, nodular type, IV Clark, 2.5 mm Breslow (**fifth primary**). Wider excision and sentinel lymph node dissection were performed, however no metastasis with immunohistochemistry for HMB-45 and S-100 and RT-PCR for Tyrosinase and MART-1, were found.

In February 2009, another lesion was found in the left eyelid, the patient underwent an excision, and histological analysis identified a basaliom (**sixth primary**).

Discussion

Multiple primary malignancies have sparked the interest of physicians, since the middle of the nineteenth century. In literature, the studies of Rokitansky⁹ in 1855, Von Bruns in 1859, and Billroth in 1869, are frequently cited. In 1932, Warren and Gates defined three criteria to identify a MPMN: 1) each of the tumors presents a definitive picture of malignancy; 2) each tumor is distinct; and 3) there's no possibility that one is a metastatic lesion derived from the other¹⁰. Another important criterion to describe MPMN, is the time elapsed between the presentation of each tumor. According to Aydine and Adnan, synchronous tumors are diagnosed within six months of the first primary tumor, and metachronous are detected after an interval of more than six months¹¹. Since Billroth first described the occurrence of multi-

ple primary malignancies in the same patient, in 1889, numerous papers have been written on the subject¹². These include case reports and voluminous accounts of as many as 1,171 cases¹³. Some reports deal with the frequency of occurrence, while others attempt to compare the incidence of second primaries to the corresponding incidence rate of the initial tumor. According to Crocetti and Buiatti, analysis of data collected from Italian Cancer Registries revealed that patients affected by cancer had, approximately, a 10% increase in risk of cancer, compared with the general population¹⁴. Although there is no definitive answer to justify this increase, the literature entertains many theories. First of all, the radiotherapical, chemotherapical or hormonal treatment are inductors to tumors, and the risk of a second primary is dramatically increased in people who underwent these types of therapies. Another possible cause is the presence of the risk factor shared between tumors (e.g. tobacco, alcohol, food). It's also possible that a genetic mutation can lead to the presentation of multiple synchronous tumors¹⁵⁻¹⁷. This eventuality is quite common and characterizes some syndromes, such as Li-Fraumeni¹⁸, and multiple endocrinal neoplasia syndromes. There is no substantial evidence to indicate that a single mutation could lead to the MPMN syndrome. Due to this lack of evidence, many recent attempts have been made to analyze the occurrence groups of MPMN, in order to identify etiologic factors. An explanation for the rise of this syndrome is that during organogenesis, some cells with a predisposition toward the development of cancer, can migrate to different organs. Later in life, carcinogenic factors might affect these cells and induce multiple primary tumors¹¹.

Speiser and Gharehbaghi-Schnell¹⁹ reported a case of a 52-year-old woman affected by seven synchronous tumors. A mutation on exon 8 of the p53 gene was found in her DNA. After an investigation of the neoplastic tissue, it was evident that there was a loss of heterozygosity for that locus¹⁹. In 1992, Lane described the importance of TP53, defining it as a "guardian of the genome", acting to protect cells from genetic damage by inducing either DNA repair or apoptosis, which appears to be an important mechanism in eliminating abnormal cells²⁰. In connection with Lane's definition, a mutation occurring on p53 can easily lead to a MPMN syndrome. So, Speiser's case seems to align perfectly with the organogenetic explanation of MPMN. This interesting case report is also strongly related to Knudson's two-hit hypothesis²¹. According to the Knudson theory, with patients affected by numerous or early tumors, one mutation is inherited via the germinal cells, and the second occurs in somatic cells. Clinical features shared by a large number of MPMN cases strengthen this hypothesis. In fact, it is clinically common that MPMN usually arise at a younger than usual age, several family members are

TABLE I - *Histological features.*

Localization	Date	Type	Grading
Left breast	13-XII-05	Infiltrating ductal carcinoma	G1 2,6 cm
15 Axillary Nodes	13-XII-05	Spread Lymphoma small B-Lymphocytes (CD20+,CD79+)	
Prostate	5-VII-07	Acinar adenocarcinoma	Gleason 5 (3+2)
Back region	18-VII-07	Pigmented, ulcerated, SSM	Clark IV, 2,35 Breslow
Preauricular region	5-X-07	Flat, round, ulcerated, NM	Clark IV, 2,5 Breslow
Basal Cell Carcinoma	27-II-09	Nodular BBC	

affected and seem to have a lower tendency to metastasize²². Although, according to these characteristics, survival usually seems to be longer than expected from the stage²³, there have been discordant opinions about the prognosis in patients with multiple primary malignancies. These varied from Peller's²⁴ protective effect of the cured tumor, to Warren and Ehreulich's²⁵ concept of specific patient susceptibility or predisposition to cancer, and Watson's¹³ statement, "*There is no demonstrable influence either of constitutional predisposition to the development of carcinoma in different organs or of any immunity resulting from the first carcinoma*". According to a review by Hubert S. and Gaskin on 42 MPMN affected patients, the most common initial primary tumor site is the breast, as it is in our case²⁶. This kind of cancer in a man is quite rare and has a bad prognosis. The number of MPMN in men affected with breast cancer is dramatically high, 12.5%. Many cancer sites are likely to be associated with treatment modalities for breast cancer. For example, organs close to the breast, such as the esophagus, lung, thyroid, and bone are likely to be affected by radiotherapy. Usually, cancer rises in the other breast, but the highest prevalence for other tumors were found for small intestine tumors and myeloid leukaemia²⁷. Secondary leukemia in patients who received chemo and/or radiotherapy for a previous malignancy is a well-documented occurrence. In the majority of cases they are represented by secondary acute myeloid leukemia (sAML), but a secondary acute lymphoblastic leukemia is possible, although less common²⁸. An interesting correlation with our case is, although not statistically significant, a twofold increased risk for melanoma among men with breast cancer (SIR= 2.00, 95% CI =0.86 to 3.94)²⁹. In a review by Cercato and Colella in 2008³⁰, only 27 cases of at least five primary malignancies were reported in English literature. Of these, 15 cases presented a skin cancer or a hematological malignancy. With this patient, both malignancies were described. The man developed two different melanomas, on two distinct body regions, a basal

cell carcinoma, and a lymphoma. A melanoma was present on the back, and on the preauricular region, and they were both diagnosed as primitive because of histological differences.

The crux of MPMN in general, and in our patient, is that tumors can affect every cellular lines, thanks to a mutation that occurs during organogenesis. This is clearly shown by the growth of different tumors in different body regions. Main features of this case report are that our patient didn't undergo radiotherapy or chemotherapy, instead, he was treated with a short hormonal therapy, as this kind of treatment could increase the risk of multiple primaries. In addition, even if primaries were not synchronous, they were detected within four years of the initial diagnosis, this is a quite short period in comparison with other analogous cases. Our patient was affected by more aggressive tumors than usual MPMN tumors, and despite the usual long-term survival of MPMN affected patients, in our case the exitus occurred after only four years from the diagnosis of the first tumor, due to melanoma metastatisation.

Research of the stem cells of the various tumors was done in blood and sentinel nodes of patients, so as to show a predisposition to develop multiple tumors. The presence of stem-cell-like tumor cells has been proposed as an alternative and/or supplemental view of newborn tumor cells. A property of stem cells is their potential for multilineage differentiation. In recent years, stem cell markers from certain tissues have been identified: in particular ALDH1 and CD 133 are considered markers of staminality for breast and prostate carcinoma³¹, whereas for melanomas, CD 133 and ABCB5 have been suggested³²⁻³³. To test the presence of stem cell markers, we verified the expression, by RT-PCR assay, of ALDH1, CD 133 and ABCB 5 in the RNA extracted from the SLN and peripheral blood of the patient.

The RNA extracted from peripheral blood, was negative for all tested markers, whereas the RT-PCR performed on RNA, extracted from the SLN, resulted positive for the expression of ABCB5, which is considered a marker of staminality for melanoma.

Conclusions

People with multiple tumors represent a segment of the cancer-survivor population, which is continuously increasing (10%). Despite this, little has been written about the experiences of this population, and more research is needed. An important area of research is the treatment of second and later cancers, as treatment for the first cancer might limit what can be given when a new cancer is diagnosed. Several genetic mutation can be involved in MPMN, our patient was positive for the expression of ABCB5, a marker for staminality of melanoma, in periphil blood.

Riassunto

La sindrome da neoplasie multiple è caratterizzata dall'insorgenza di diversi tumori in maniera sincroma in un organismo. Il caso da noi riportato ha evidenziato la presenza di sei diverse neoplasie primarie nell'arco di quattro anni. Il paziente è stato affetto da adenocarcinoma prostatico, carcinoma duttale mammario, linfoma (CD 20+), due melanomi indipendenti e un basalioma. È stata, quindi, effettuata la ricerca di marker di staminalità nel sangue periferico e nei linfonodi sentinella, dimostrando la presenza del recettore ABCB5, tipico del melanoma.

References

- 1) Billroth T: *Die)Allgemein Chirurgische Pathologie und therapie in 51 Vorlesungen*. In: *Handbuch fur Studienende and artze*. 4 Berlin: Auflage; p 908.
- 2) Teppo L, Pukkala E, Saxen E: *Multiple cancer an epidemiological exercise in Finland*. J Nat Cancer Inst, 1985; 75:207-11.
- 3) Berg JW, Schottenfeld D: *Multiple primary cancers at Memorial Hospital 1949-1962*. Cancer, 1977; 40 (suppl): 1801-805.
- 4) Flannery JT, Boice JD, et al: *Cancer registration in Connecticut and the study of multiple primary cancers, 1935-82*. Natl Cancer inst Monogr, 1987; 68:13-24.
- 5) Levi F, Randimbison L, Te VC, et al.: *Multiple primary cancers in the Vaud Cancer Registry, Switzerland, 1974-89*. Br J Cancer, 1993; 67:391-95.
- 6) Ries LA, Eisner MP, Kosary CL, et al.: *SEER cancer statistics review. 1975-2000*. Bethesda National Cancer Institute, 2003
- 7) Mariotto AB, Rowland JH, Ries LA, et al.: *Multiple cancer prevalence: A growing challenge in long-term survivorship*. Cancer Epidemiol Biomarkers Prev, 2007; 16(3):566-71.
- 8) Romics L jr, O'Brien MN, Relihan N, et al.: *Intracystic papillary carcinoma in a male as a rare presentation of breast cancer: a case report and literature review*. J med case reports, 2009; 13(3):13.
- 10) Mercanton F: *Des carcinomes primaries multiple*. Rev Med Suisse Rom, 1893; 13:173, 229.
- 11) Warren S, Gates O: *Multiple primary malignant tumors, a survy of the literature and statistical study*. Am J Cancer, 1932; 16:1358-414.
- 12) Aydiner, Adnan MD, Karadeniz, et al.: *Multiple primary Neoplasm at a single institution: Differences between synchronous and metachronous neoplasm*. Am Journ Clin Oncol: cancer clinical trials, 2000; 23(4), 364-70.
- 13) Savage D: *A family history of uterine and gastrointestinal cancer*. Br Med J, 1956; 2:341-43.
- 14) Watson TA: *Incidence of multiple cancer*. Cancer, 1953; 6:365-71.
- 15) Crocetti E, Buiatti E, Falini P and the Italian Multiple Primary Cancer Group: *Multiple primary cancer incidence in Italy*. Eur J cancer, 2001; 37:2449-456.
- 16) Li P, Fraumeni JF: *Prospective study of a family cancer syndrome*. JAMA, 1982; 247:2692-694.
- 17) Miki Y, Swensen J: *A strong candidate for the breast and ovarian cancer susceptibility gene, BRCA2, to cromosome 13q12-13*. Science, 1994; 265:2088-90.
- 18) Varely JM, Evans DGR, Birch JM: *Li-Fraumeni syndrome: A mulecular and clinical review*. Br J Cancer. 1997; 76:1-14.
- 19) Li FP, Fraumeni JF Jr: *Soft-tissue sarcomas, breast cancer, and other neoplasms. A familial syndrome?* Ann Intern Med , 1969; 71:747-52.
- 20) Speiser P, Gharehbaghi-Schnell E, Eder S, et al.: *A constitutional de novo mutation in exon 8 of the p53 gene in a patient with multiple primary malignancies*. Br J Cancer, 1996; 74(2):269-73.
- 21) Lane DP: *P53, guardian of the genome*. Nature, 358; 15-16.
- 22) Knudson AG Jr: *Mutation and cancer: Statistical study of retinoblastoma*. Proc Natl Acad Sci USA, 1971;68(4):820-23.
- 23) Taylor TV, Torrance B: *Behaviour of multiple primary neoplasm*. Br Med J, 1977.
- 24) Baigrie RJ: *Seven different primary cancers in a single patient. A case report and review of multiple primary malignant neoplasia*. Eur J Surg Oncol, 1991; 17(1):81-83.
- 25) Peller S: *Metachronous Multiple Malignancies in 5,876 cancer patients*. Amer J Hyg, 1941; 34:1.
- 26) Warren S, Ehrenreich T: *Multiple primary malignant tumors and susceptibility to cancer*. Cancer Res, 1944; 4:554.
- 27) Gaskin HS, Hardy RE, Fletcher RL: *Multiple primary malignancies in black patients*. J Natl Med Assoc, 1981; 73(11): 1065- 68.
- 28) Hemminki K, Scélo G, Boffetta P, et al.: *Second primary malignancies in patients with breast cancer*. Br J Cancer, 2005; 92(7):1288-92.
- 29) Pagano L, Pulsoni A, Mele L, et al and Gruppo Italiano Malattie Ematologiche dell'Adulto: *Acute myeloid leukemia in patients previously diagnosed with breast cancer: experience of the GIMEMA*. Ann Oncol, 2001; 12(2):203-7.
- 30) Auvinen A, Curtis RE, Ron E: *Risk of subsequent cancer following breast cancer in men*. Journ Nat Canc Inst, 2002; 94 (17): 1330-332.
- 31) Cercato MC, Colella E, Ferraresi V, et al.: *Report of two cases of quintuple primary malignancies and review of the literature*. Anticancer Res, 2008; 28(5B):2953-958.

- 32) Boman BM, Wicha MS: *Cancer stem cells: A step toward the cure*. J Clin Oncol, 2008; 26(17):2795-799.
- 33) Frank NY, Pendse SS, Lapchak PH et al.: *Regulation of progenitor cell fusion by ABCB5 Pglycoprotein, A novel human ATP-binding cassette transporter*. J Biol Chem, 2003; 278:47156- 7165.
- 34) Frank NY, Margaryan A, Huang Y. et al.: *ABCB5-mediated doxorubicin transport and chemoresistance in human malignant melanoma*. Cancer Res, 2005; 65:4320-333.

