CASE REPORT

Quadruple Cancers of Non-producing Multiple Myeloma, Cholangiocellular Carcinoma, and Two Different Thyroid Cancers

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Abstract

We report the case of a 72-year-old man who presented with non-producing multiple myeloma (MM) with three additional concomitant solid tumors that were identified by postmortem autopsy. The disease was refractory to anti-MM therapy including bortezomib and lenalidomide, and he finally died of bacterial pneumonia with diffuse alveolar damage 8 months after the diagnosis. An autopsy revealed that he was also affected by three other solid cancers, cholangiocellular carcinoma, medullary thyroid cancer and papillary thyroid cancer that were clinically asymptomatic and remained undiagnosed before death. A review of the literature suggests that primary quadruple cancers including MM are extremely rare.

Key words: non-producing multiple myeloma, quadruple cancer, autopsy

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Introduction

Multiple myeloma (MM) is the second most common hematologic neoplasm of clonal malignant plasma cells, and it is known to cause a series of related-organ or tissue impairments, such as skeletal destruction with bone pain and pathological fractures, hypercalcemia, renal insufficiency, anemia, or hyperviscosity (1). In addition, most likely due to the combined impairment of both the humoral immune response and cell-mediated immunity, a tendency to occur in the elderly, and exposure to cytotoxic agents, MM patients occasionally exhibit the co-emergence of other cancers. We herein report a rare case of primary quadruple cancers with non-producing type MM, and review the literature regarding more than three concomitant primary cancers including MM.

Case Report

A 72-year-old man was admitted to our hospital complaining of general fatigue and intractable pain in his neck and back, despite the use of analgesic drugs for two months. He had no prior history of radiation exposure or cytotoxic agents. Radiologic examinations revealed that he had diffuse and multiple lytic lesions in the vertebrae, ribs, sternum, and pelvic bone, and vertebral compression fractures (Th5, 6). A blood examination showed anemia, hemoglobin 12.3 g/dL, low proteinemia of 5.8 g/dL, hypogammaglobulinemia [serum immunoglobulin (Ig) G 340 mg/dL, IgA 3 mg/dL, IgM <3 mg/dL], elevated β2 microglobulin of 7.91 mg/dL, and the presence of abnormal plasma cells (total leukocyte count 22.0×10⁶/L including 11.0% of abnormal plasma cells). An immunoprecipitation analysis and serum free light chain analysis indicated the absence of monoclonal protein in his
nuclei. Surprisingly, three concomitant solid tumors were identified by culturing of the lung tissues. BM histology revealed a diffuse proliferation of abnormal plasma cells including multinuclear giant cells with densely stained nuclei. Despite treatment with broad-spectrum antibiotics, antifungal, antiviral, and methylprednisolone pulse therapy, he eventually died of respiratory failure 8 months after the initial diagnosis of MM.

An autopsy was performed with the informed consent from his family. The bilateral lungs showed diffuse alveolar damage in the proliferative phase and several types of bacteria were identified by culturing of the lung tissues. BM histology revealed a diffuse proliferation of abnormal plasma cells including multinuclear giant cells with densely stained nuclei. Surprisingly, three concomitant solid tumors were detected; one in his liver and two in the thyroid that were clinically asymptomatic and remained undiagnosed before his death. The tumor detected in the right lobe of the liver measured about 4 cm in diameter (Fig. 2A), and a histologic examination showed the tumor to be moderately- or poorly-differentiated cholangiocellular carcinoma, which was positive for CK7, CK19, Alcian-blue, but was negative for alpha fetoprotein (Fig. 1B, C). One of two thyroid tumors in the right lobe measured about 5 mm in diameter and the other in the left lobe was less than 1 mm in diameter (Fig. 2B, C). A histologic examination revealed the former to be medullary thyroid cancer, which was positive for calcitonin and carcinoembryonic antigen (Fig. 1D, E), while the latter was papillary thyroid cancer (Fig. 1F).

**Discussion**

Multiple primary cancers (MPCs) have been defined as two or more histologically different malignant cancers that develop independently without a common etiology (2), and the present case fulfilled this definition. Along with the progressive aging of the population and the prolongation of the survival of MM patients, due to improvements in the treatment strategy, the number of MM patients with concomitant cancer(s) will most likely increase. However, information about MPCs including MM has been limited. In particular, information regarding triple or quadruple MPCs including MM remains rather limited.

While previous studies have shown the incidence of triple or more MPCs to be 1.1% and that of quadruple MPCs to
be 0.007% in autopsy cases of various cancers (3, 4), the incidence of more than triple MPCs has been reported to be 0.03-1.4% in MM (5, 6). However, as far as we could determine based on a search of the pertinent literature, there have been no case reports of more than quadruple MPCs including MM (Table). MPC has been subcategorized into two

Table. Details of MM Patients with Two Or Three Additional Different Neoplasms.

| Age at diagnosis of MM and gender | Date of diagnosis of MM | Type of DNs | Date of diagnosis of DNs | Time of occurrence of DNs compared with MM | Ref. |
|----------------------------------|-------------------------|-------------|--------------------------|------------------------------------------|------|
| 67/m                             | 11/2005                 | Prostate cancer, Bladder cancer | 1/1998, 1/1999 | M/Pri | (5) |
| 57/f                             | 10/2003                 | Colon cancer, Melanoma | 7/1976, 1/1998 | M/Pri | (5) |
| 66/m                             | 9/2007                  | Prostate cancer, MCL | 10/2005, 11/2005 | M/Pri | (5) |
| 55/m                             | 10/1985                 | Bladder cancer, Colon cancer | 7/1981, 5/1999 | M/Pri, M/Sub | (5) |
| 72/f                             | 10/2003                 | Liposarcoma, t-AML | 1/2000, 12/2005 | M/Pri | (5) |
| 73/f                             | 6/2006                  | Colon cancer, t-MDS | 6/2000, 9/2007 | M/Pri, M/Sub | (5) |
| 66/m                             | 5/1988                  | Prostate cancer, Colon cancer | 3/1996, 8/2001 | M/Sub | (5) |
| 77/m                             | 1/2006                  | CLL, t-AML | 1/2006, 6/2007 | Syn, M/Sub | (5) |
| 70/m                             | 4/2009                  | HCL, Prostate cancer | 1/1999, 1/1997 | M/Pri | (6) |
| 86/m                             | 1/2009                  | Colon cancer, Bladder cancer | 5/2005, 1/2004 | M/Pri | (6) |
| 77/m                             | 1/2010                  | Melanoma, Prostate cancer | 1/2008, 1/1995 | M/Pri | (6) |
| 80/m                             | 3/2003                  | Epiglottic cancer, Prostate cancer | 1/1999, 8/1999 | M/Pri | (6) |
| 77/m                             | 1/2001                  | Prostate cancer, Lung cancer | 1/1988, 2/2009 | M/Pri, M/Sub | (6) |
| 82/m                             | 3/2009                  | Bladder cancer, Lung cancer | 10/2001, 1/2007 | M/Pri | (6) |
| 72/m                             | 11/2012                 | Cholangiocellular carcinoma, Medullary thyroid cancer, Papillary thyroid cancer | 5/2013, 5/2013 | Syn, Syn | (6) |

m: male, f: female, MM: multiple myeloma, DNs: different other neoplasms, M: metachronous, Syn: synchronous (diagnosis of MM and DNs diagnosed within 6 month), Pri: prior (diagnosis of DNs more than 6 month before diagnosis of MM), Sub: subsequent (diagnosis of DNs more than 6 month after diagnosis of MM), MCL: mantle cell lymphoma, t-: therapy related, AML: acute myeloid leukemia, MDS: myelodysplastic syndrome, CLL: chronic lymphoid leukemia, HCL: hairy cell leukemia

Figure 2. Macroscopic view of the postmortem examination of the liver and thyroid. A single liver tumor (A) and two thyroid tumors (B: right lobe and C: left lobe, arrowhead) were identified.
types based on the timing of diagnosis, i.e., one is “synchronous” MPC that have more than two cancers diagnosed within six months, and the other is “metachronous” MPC, in which the timing of the diagnoses of different cancers are more than six months apart (7). When we subcategorized 31 cancers detected with MM in our patient and 14 reported patients with triple MPCs, the number of the metachronous cancers and the synchronous cancers were 27 and 4, respectively. In addition, among the 27 metachronous cancers, twenty were diagnosed before the diagnosis of MM. In our case, it is possible that the thyroid cancers might have existed before the diagnosis of MM, as the retrospective review of computed tomography (CT) at his admission suggested the presence of a small nodule in his thyroid. In contrast, the liver tumor was not identifiable by CT examination upon admission; thus the cholangiocellular carcinoma grew rapidly during the treatment for MM.

In our case, the cancer types included 7 prostate cancer, 5 colon cancer, 4 bladder cancer, 3 myeloid malignancies, 3 lymphoid malignancies, 2 lung cancers, and other. While high frequencies of prostate cancer, colon cancer and bladder cancer may associated with the elder predominance of MM, it is reasonable to assume that myeloid malignancies could occur after the diagnosis of MM, considering the toxic influence of cytotoxic agents for MM on hematopoietic cells. In contrast to myeloid malignancies, three lymphoid malignancies occurred before or together with the diagnosis of MM. As far as we searched, we could not find any reports showing the difference of frequency of MPC among MM subtypes, according to M-protein types or genetic/cytogenetic abnormalities. In contrast with hereditary MPCs, such as multiple endocrine neoplasia or Li-Fraumeni syndrome, the direct etiological association among MM and other cancers in patients with more than triple MPCs has been lacking. Therefore, further investigation is needed to identify the possible association between inheritable genetic polymorphisms and environmental stress, which may cause MPCs including MM in the elderly.

In conclusion, we herein described a rare case of primary quadruple cancers including non-producing MM. Our case and review of the pertinent literature suggest the need for general screening to search for other concomitant cancers in the daily clinical practice of MM.

The authors state that they have no Conflict of Interest (COI).

References

1. The International Myeloma Working G. Criteria for the classification of monoclonal gammapathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. Br J Haematol 121: 749-757, 2003.
2. Warren S, Gars O. Multiple primary malignant tumors. A survey of the literature and a statistical study. Am J Cancer 16: 1358-1414, 1932.
3. Watanabe S, Kodama T, Shimosato Y, et al. Multiple primary cancers in 5,456 autopsy cases in the National Cancer Center of Japan. J Natl Cancer Inst 72: 1021-1027, 1984.
4. Nakayama H, Masuda H, Ugajin W, et al. Quadruple cancer including bilateral breasts, Vater’s papilla, and urinary bladder: Report of a case. Surg Today 29: 276-279, 1999.
5. Hasskarl J, Ihorst G, De Pasquale D, et al. Association of multiple myeloma with different neoplasms: systematic analysis in consecutive patients with myeloma. Leuk Lymphoma 52: 247-259, 2011.
6. Munker R, Shi R, Lin D, Guo S, Hayes TG. Multiple myeloma and other malignancies: a pilot study from the Houston VA. Clin Lymphoma Myeloma Leuk 14: 102-106, 2014.
7. Moertel CG, Dockerty MB, Baggenstoss AH. Multiple primary malignant neoplasms. II. Tumors of different tissues or organs. Cancer 14: 231-237, 1961.