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Annals of Diagnostic Pathology 16 (2012) 515 – 520

Annals of DIAGNOSTIC PATHOLOGY

A patient with prostate cancer and multiple myeloma—diagnostics and possible association of both diseases

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Abstract In this report, we describe a case of a patient with prostate cancer and multiple myeloma as the second metachronous malignant disease. To our knowledge, synchronous occurrence of bone marrow prostate cancer metastases and multiple myeloma—as it was found in the clinical disease course of our patient—has not been documented in the literature. Among other diagnostic procedures, cytomorphology and immunocytochemistry analyses contribute to detection of metastases of epithelial cells and synchronous plasma cell proliferation in bone marrow. Occurrence of multiple myeloma and prostate cancer in our patient adds to other similar reports and points to possible association between both diseases and also to other factors involved in the development of a second malignant disease. Further studies are needed to confirm and clarify this association, because prostate cancer is a relatively common malignant disease.

Keywords: Prostate cancer; Multiple myeloma; Second cancer; Gleason score; Prostate-specific antigen; Immunocytochemistry

1. Introduction

Prostate adenocarcinoma, the most frequent cancer of the prostate accounting for 98% of all primary prostate tumors, is associated with elevated serum prostate-specific antigen (PSA) [1,2]. The spectrum of differentiation of prostate adenocarcinoma could be presented in several grading systems; the most widely used is Gleason grading system based on 5 histologic patterns of tumor gland formation and stroma infiltration [1,3]. Many factors have been proposed to be connected with the development of prostate adenocarcinoma. The presence of androgens and advanced age are the most accepted risk factors [4]. Prostate intraepithelial neoplasia is a precursor lesion that precedes prostate adenocarcinoma by about 10 years [1].

Multiple myeloma (MM) is multifocal plasma cell neoplasm usually presenting with multiple osteolytic bone lesions, bone marrow (BM) plasma cell infiltration, serum monoclonal gammopathy, Bence Jones proteinuria, and reduced normal polyclonal immunoglobulins. Other laboratory findings include hypercalcemia, elevated creatinine, hyperuricemia, and hypoalbuminemia. Chronic antigen stimulation from infection or other chronic disease and exposure to specific toxic substances or radiation have been associated with an increased incidence of MM [5]. A premalignant lesion, monoclonal gammopathy of undetermined significance, which is present in 1% of adults, may progress to MM at a rate of 1% per year [6].

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1092-9134/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.anndiagpath.2011.04.010

Malignant tumors, as well as multiple synchronous or metachronous cancers, can be associated with genetic, environmental, and occupational factors or with Epstein-Barr and *Helicobacter pylori* infection, immunodeficiency, and ultraviolet radiation and are more frequently observed in patients after cytostatic or radiation therapy [7,8]. Thus, there are reports of patients with metachronous or synchronous occurrence of MM and prostate cancer [7-11]. However, to our knowledge, it was not described in a patient with prostate cancer BM metastases and synchronous occurrence of MM, as in the presented case of our patient. Diagnostic indicators of both diseases in our patient are documented, and possible association based on the literature data is also described.

2. Case report

Prostate cancer was diagnosed in February 2005 in a 63-year-old man by prostate core needle biopsy. Histopathology revealed adenocarcinoma, with a Gleason score of 4 + 5 = 9 in both lobes. High serum PSA level (232 μg/L) was detected before biopsy, pointing to metastatic disease with high probability. However, plain chest radiology, computed tomography imaging of pelvis, and radioisotope bone scan were negative for metastases. Neoadjuvant hormonal treatment consisting of goserelin acetate and flutamide was started immediately. From July until September 2005, external irradiation was performed on linear accelerator manufactured by Siemens. Two-dimensional high-energy radiation technique was applied. The whole pelvis was irradiated with tumor dose (TD) 5040 cGy in 28 fractions, daily dose TD 180 cGy, and after that, 2000 cGy in 10 fractions was applied to the prostate with reduced fields. Combined hormonal treatment was continued concurrently with radiotherapy. After irradiation and hormonal treatment, PSA level decreased to 0.2 μg/L and remained around that level up to end of year 2006. In January 2007, bilateral orchiectomy was performed due to elevation of PSA (2.48 μg/L). In March 2008, it was evident that the disease turned to hormonal-resistant stage, so the treatment was further continued with chemotherapy; 2 cycles of carboplatin were applied but with no clinical benefit. Second-line chemotherapy was mitoxantrone plus decortin (prednisone), 6 cycles. At that time, bone scan revealed multiple mixed osteolytic and osteoblastic bone metastases, and bisphosphonate Zometa (zoledronic acid; Novartis, Zagreb, Croatia) was incorporated in the treatment.

An increase in PSA (131.9 μg/L) in our patient in August 2008 (3 years after the diagnosis) was detected, implicating progression of the disease. Spine x-rays showed multiple osteolytic lesions uncharacteristic for prostate cancer metastases, and unyielding thrombocytopenia grade 2 was observed for the first time. Thus, BM aspiration was done because of multiple osteolytic spine lesions and persistent thrombocytopenia. Cytologic analysis of BM revealed proliferation of plasma cells and metastases—clusters of malignant epithelial cells. Other laboratory findings also confirmed MM as secondary malignant disease: elevated total serum proteins (97 g/L), M protein (immunoglobulin [Ig] G 47.97 g/L), and high β2-microglobulin (3.5 mg/L) were found, as well as increase in the kappa/lambda serum ratio (53.3). Serum calcium was within reference range (2.29 mmol/L; reference range, 2.14-2.53 mmol/L), whereas the patient was treated with Zometa because of previously diagnosed bone metastases. The patient was treated with 40 mg dexamethasone for 4 days per month and 100 mg thalidomide per day with response to MM therapy and reduction in BM plasma cell number, but with persistent clusters of malignant epithelial cells in BM. A decrease in total serum proteins (61 g/L) and IgG (8.37 g/L) was also documented. Unfortunately, 14 months after diagnosis of MM as the second malignant disease, severe cachexia occurred, and the patient died because of prostate cancer dissemination.

2.1. Pathohistologic findings

Histologic features of adenocarcinoma were found in all 6 core needle biopsy specimens taken from the left and right prostate lobes. The tumor tissue consisted of abnormal infiltrative small glandular arrangements with a single cell layer of intermediate to high polymorphic carcinoma cells. Most of adenocarcinoma tissue was composed of cribriform atypical glands (the most common pattern), and signet-ring cells (the worst component) were found in the same acinar tumor structures. Gleason score was 4 + 5 = 9 in both prostate lobes based on the most common pattern of 4 and signet-ring cell component of 5 (Figs. 1 and 2) [3].

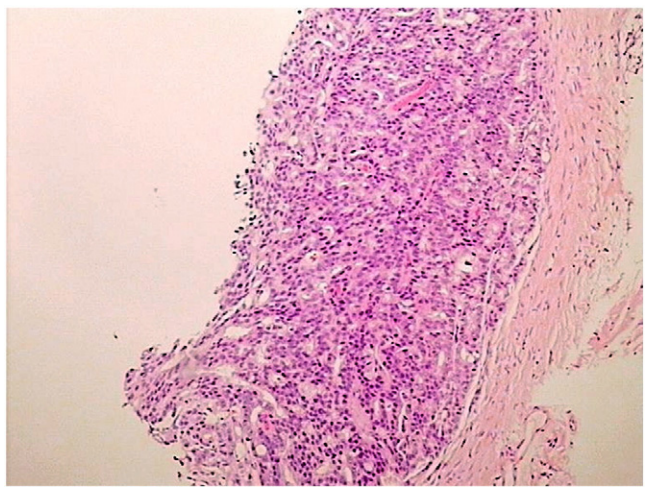

Fig. 1. Adenocarcinoma of the prostate: Gleason pattern 4 with small glands, glands fusion, and cribriform type (hematoxylin and eosin, medium power ×200).

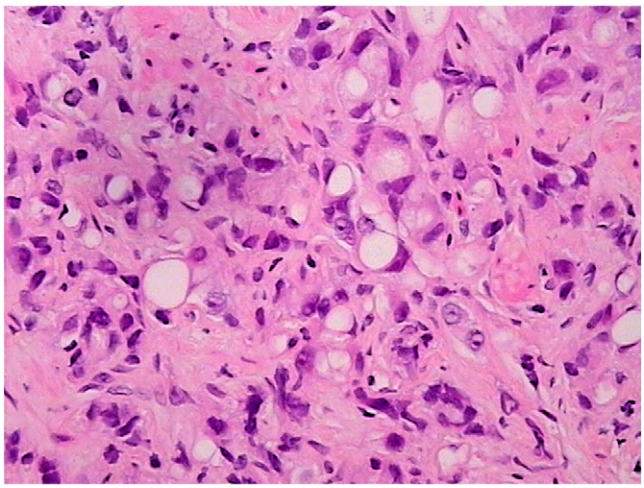

Fig. 2. Adenocarcinoma of the prostate with signet-ring cell-like features (hematoxylin and eosin, high power ×400).

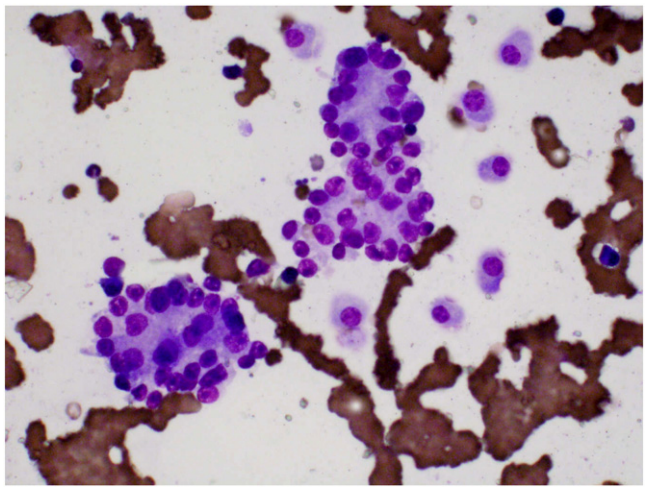

Fig. 4. The clusters of malignant epithelial cells and few plasmocytes (Pappenheim, high power ×400).

2.2. Cytomorphologic and immunocytochemical findings

Three years after the diagnosis of prostate cancer, cytologic analysis of BM revealed numerous plasmocytes comprising 50% to 80% of all nucleated BM cells (Fig. 3). The clusters of well- and moderately differentiated carcinoma cells were also found in BM besides plasma cell proliferation (Fig. 4). After labeled streptavidin-avidin biotin (LSAB) immunostaining, immunocytochemical analysis of BM cells confirmed both carcinoma metastases and MM as the secondary malignant disease. Almost all plasma cells were CD38 and CD138 positive (Fig. 5) and, as expected, negative for cytokeratin and Ber-EP4. The carcinoma cells were positive for cytokeratin (Fig. 6) and Ber-EP4 and negative for CD38, CD138, and LCA. The patient was followed in the course of further treatment, and BM cytologic specimens after 5 months revealed a reduced number of plasmocytes (6%–12% of all nucleated BM cells) with persistent clusters of malignant epithelial cells.

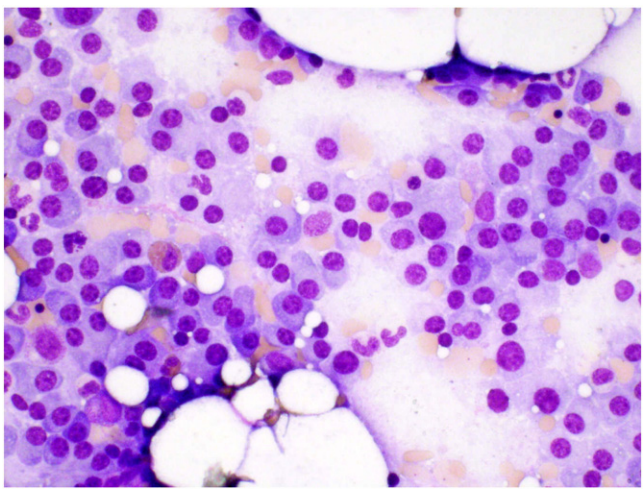

Fig. 3. Numerous plasmocytes in BM (Pappenheim, high power ×400).

3. Discussion

3.1. Diagnostic indicators

In healthy people, PSA reference interval of 0 to 4 μg/L has been reported using a commercial prototype test. Because PSA increases with age, different age-specific upper reference limits have been reported, that is, 2.5 (40-49 years), 3.5 (50-59 years), 4.5 (60-69 years), and 6.5 μg/L (70-79 years) [1,2,12]. In our patient, the very high level of PSA (232 μg/L) pointed undoubtedly to prostate cancer [2,12]. Suspected adenocarcinoma was confirmed by

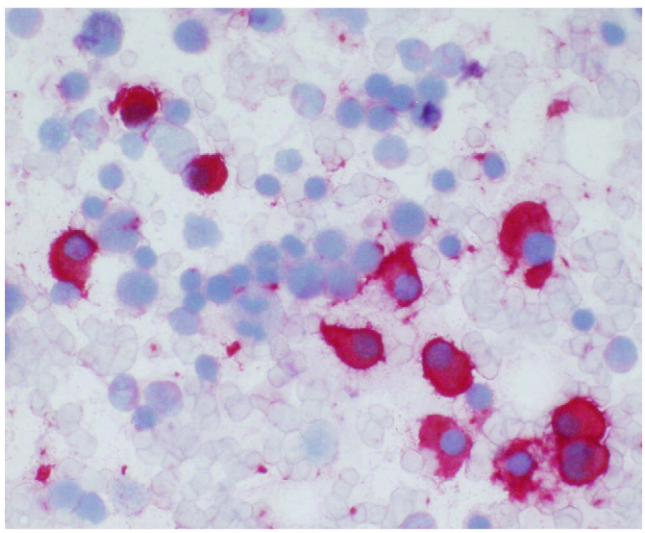

Fig. 5. CD138-positive plasmocytes and 2 clusters of CD138-negative malignant epithelial cells (LSAB, high power ×400).

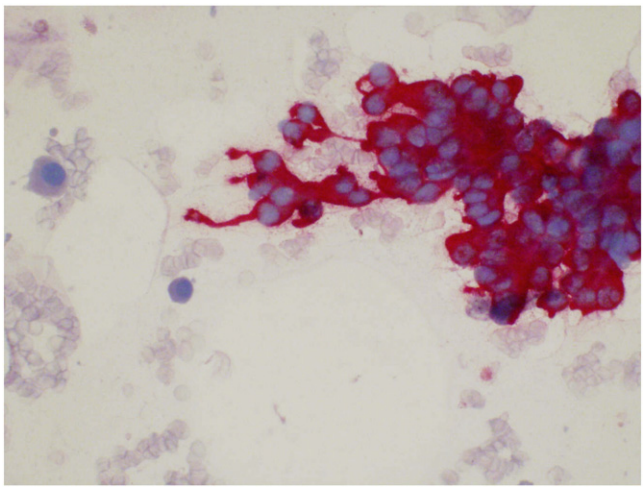

Fig. 6. A cluster of cytokeratin-positive malignant epithelial cells and 2 cytokeratin-negative plasmocytes (LSAB, high power ×400).

histopathology on core biopsy specimens, and Gleason score 4 + 5 = 9 was estimated in both prostate lobes (Figs. 1 and 2). The most significant prognostic factors in prostate cancer are Gleason score, tumor volume, surgical margins, capsular invasion, and Ki-67 index [1-3,13-15]. Thus, for patients with Gleason score 7 and above, as found in our patient, the probability of progression-free survival is lower in comparison with patients with Gleason score 6 and below [14]. Moreover, multifocal prostate cancer, cribriform adenocarcinoma pattern, and signet-ring cells, the findings that were all established in our patient, are usually associated with high grade, high stage, high recurrence rate, and poor prognosis of disease [13,14].

Serum PSA level is the essential pretreatment prognostic factor and also a prognostic indicator of outcome after radiotherapy because the rising PSA level, found in our patient, implicated clinical recurrence or progression of the disease [1,2,14,15]. Thus, low PSA level (about 0.2 μg/L) in our patient after irradiation and hormonal treatment was followed by elevation of PSA (2.48 μg/L), suggesting that the disease turned to hormonal-resistant stage; the suspected progression of disease was also confirmed by radiologic detection of osteolytic and osteoblastic bone metastases. Despite chemotherapy treatment in our patient, further progression of the disease occurred 3 years after the diagnosis because of significant PSA increase (131.9 μg/L), spine osteolytic lesions on plain radiology, and persistent thrombocytopenia. However, only 5% of prostate cancer bone metastases are osteolytic, and therefore, the second malignant disease was also suspected. Cytologic BM analysis confirmed the progression of disease, that is, metastases of carcinoma cells and also MM as the second hematologic malignant disease.

Monoclonal gammopathy is frequently associated with lymphoproliferative disease of the B-cell origin (MM, lymphoplasmacytic lymphoma, and chronic lymphocytic leukemia) [5]. There is also established occurrence of elevated IgG, IgA, or IgM in patients with epithelial neoplasia because of the second neoplasia of B lymphoid cells, as was the case in our patient [10]. However, monoclonal gammopathy could be observed not only due to neoplastic B-cell proliferation but also as part of immunologic changes in patients with malignant tumor of epithelial origin. In patients with epithelial neoplasia, a host's reaction is known to occur that involves T killers, T helpers, and B lymphocytes, and the low levels of M protein might be a result of lymphoid B-cell activation and antitumor immune response [16]. Moreover, a possibility that the IgG is produced by epithelial cancer cells has been confirmed in recently published studies documenting IgG secretion directly from cancer epithelial cells, which are involved in tumor growth and survival [17].

Like normal plasma cells, most MM plasmocytes usually express CD79, and they are also, as in our patient, strongly positive for CD138 (collagen-1–binding proteoglycan, syndecan 1; Fig. 5) and CD38. Cytokeratins and other epithelial markers (ie, Ber-EP4) are positive in malignant epithelial cells (as in the clusters of the carcinoma cells found in the BM of our patient; Fig. 6) and generally negative in MM plasmocytes [5].

3.2. Incidence and possible association of MM and prostate cancer

Incidence of multiple cancers varies in different patient populations and is related to geographical, race, age, environmental, occupational, and genetic population factors, as well as to the type, site, and number of primary cancers, and is also associated to previous cytostatic or radiation therapy [7,8]. In the 2002 to 2006 period, annual incidence of prostate cancer in United States was 159.3 per 100 000 men [18]. The incidence of MM in the general population is 4 per 100 000 per year [18]. Moreover, according to some studies, there appears to be an increased incidence of MM among patients with prostate cancer. Thus, in a study of Kao et al [19] among 700 consecutive patients with prostate cancer, there were 4 cases of MM that preceded the diagnosis of prostate cancer. Based on MM incidence in the general population (4 per 100 000), only 0.028 cases of MM are expected in 700 patients with prostate cancer. Increased risk of MM was observed in individuals whose first-degree relatives had other types of tumors, especially if they occurred in the prostate or brain [10,11].

Moreover, studies analyzing possible association of MM and prostate cancer have pointed to susceptibility to other hematologic malignancies and a second solid tumor including prostate cancer in most hereditary cancer syndromes and familial MM [7,8,10,11]. Besides genetic events, one of the possible explanations for such connection is that MM may produce a microenvironment or immune dysfunction favoring progression of prostate intraepithelial neoplasia or latent cancer to clinically evident prostate cancer [19]. However, Kristinsson et al

[20] could not confirm in a recent study the possible risk of prostate cancer in patients with monoclonal gammopathy of undetermined significance, a precursor lesion of MM, as established in their previous studies.

Linkage analysis of hereditary prostate cancer has suggested several candidate genes (loci on chromosomes 1, X, and 17) [19]. The most frequent chromosome translocations in MM involve the heavy-chain locus (IGH@) on chromosome 14q32. Translocations of 14q32 involve 5 major oncogens: cyclin D1 (11q13), C-MAF (16q23.1), FGFR3 (4p16.3), cyclin D3 (6p21), and MAFB (20q11) [5]. It is, however, interesting that karyotypes of MM are also complex; both numerical and structural chromosome abnormalities have been found and are more similar to those found in epithelial tumors and the blast phase of chronic myeloid leukemia [21]. Moreover, homozygous deletions in various adenocarcinomas (ie, breast and prostate cancer) and t(14;16) chromosomal translocations in MM are near, or associated with, fragile site FRA 16D (16q23.2) found within regions of frequent loss of heterozygosity that is connected with DNA instability and to altered expression of associated genes in neoplasia [22,23].

Although genetic events appear to play the key role in initiation and progression of plasma cell myeloma, the BM microenvironment factors (extracellular matrix proteins, secreted cytokines and growth factors, interaction of the BM stromal cells) are also important in pathogenesis and progression of MM [19]. It is also interesting that microenvironment in prostate cancer and MM showed important similarities and that certain cytokines are involved in neoplastic transformation and clinical course of both diseases [19]. Interleukin 6, an essential activating growth factor and antiapoptotic agent of MM, is also essential in signaling the mitogen-activated protein kinase pathway in prostate cancer [24]. Insulinlike growth factor 1 is also a potent growth factor that increases proliferation of MM plasmocytes and is also involved in progression of prostate cancer [19]. Vascular endothelial growth factor, secreted by some myeloma cell lines, is an important mediator of angiogenesis in MM and prostate cancer [25]. Stromal-derived factor 1 was found to be a chemoattractant factor causing the selective adhesion of myeloma cells to the bone, enhancing their proliferation. Stromal-derived factor 1 was also shown to be a chemoattractant for metastasis of prostate cancer cells to the bone [26]. Thus, it may be possible that the development of MM in our patient as a secondary malignant disease enhanced the progression of prostate cancer and metastasis to the bone.

In conclusion, cytomorphology and immunocytochemistry analyses contribute to the detection of MM plasmocytes and metastases of epithelial cells in BM, allowing accurate diagnosis of both prostate BM cancer metastases and MM as the secondary malignant disease. The occurrence of MM and prostate cancer in our patient adds to other similar reports and also points to possible association between MM and prostate cancer. However, because other factors (primarily cytostatic and radiation therapy) could be involved in the occurrence of the second cancer and because prostate cancer is a relatively common malignant disease, further studies are needed to confirm and clarify this association.

Acknowledgments

We thank Nikola Habuzin, BA, for his assistance in preparing the English version of the manuscript.

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