Review

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Association between Prostate Carcinoma and Multiple Myeloma

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Synchronous or sequential development of multiple myeloma and prostate carcinoma is rare. It is not sure whether these two occur independently or if one influences the development of the other. We reviewed the cases published in the English literature; eight cases of myeloma developing after diagnosis and treatment for prostate carcinoma, five cases of simultaneous occurrence of myeloma and prostate carcinoma, and five cases where the patient with multiple myeloma later developed prostate carcinoma were found. This short review attempts to analyze the occurrence of these two diseases in the same patient and dissect whether there is a close association or it is just a mere coincidence.

Keywords: prostate cancer; multiple myeloma; co-occurrence; plasma cell neoplasm; synchronous

Introduction

Prostate cancer is a common malignancy that affects the prostate gland in men. It typically develops slowly and often remains localized within the gland, but it can metastasize to other parts of the body if left untreated. Risk factors for prostate cancer include age, family history, and certain genetic mutations. Manifested in the bone marrow as a clonal proliferation of plasma cells, multiple myeloma (MM) is a hematological malignancy. It is the second most common blood cancer and accounts for significant morbidity and mortality worldwide [1]. The disease is associated with symptoms such as bone pain, anemia, renal dysfunction, and hypercalcemia. Treatment options include chemotherapy, immunomodulatory drugs, proteasome inhibitors, and stem cell transplantation [1].

The coexistence of prostate cancer and MM in a single patient is an infrequent occurrence with only a handful of cases reported in the English literature. Synchronous bone marrow involvement by both these malignancies is even rarer [2–13]. The relationship between these two disorders is not well understood. However, major similarities between the bone marrow microenvironments (BMME) involved in both of these malignancies have been implicated as a possible explanation. BMME comprises cellular and non-cellular compartments. The cellular compartment consists of stroma, osteoblasts, immune cells, osteoclasts, and endothelial cells. The non-cellular compartment is composed of growth factors, cytokines, extracellular matrix (ECM), and chemokines. It is suggested that the BMME may play an important role in the occurrence of these malignancies together [2]. As per our search in the English literature, we were able to find 8 cases where patients with prostate carcinoma later developed MM (Table 1) [3–8,14], 5 cases where prostate carcinoma and MM were diagnosed together (Table 2) [2,9–12] and 5 cases where the patient with MM later developed prostate carcinoma (Table 3) [13,15] In this article, we have reviewed and analyzed the existing cases of prostate cancer and MM occurring in the same individual.

Materials and Methods

Given there were no specific statistical data on prostate cancer and MM in the same individual, PubMed, and Google Scholar records reporting a diagnosis of such, including available case reports and case series were reviewed. Out of the total of 18 cases, there were 8 cases where patients with prostate carcinoma later developed MM (Table 1) [3–8,14], 5 cases where prostate carcinoma and MM were diagnosed together (Table 2) [2,9–12], and 5 cases where the patient with MM later developed prostate carcinoma (Table 3) [13,15] were found. These cases were analyzed.

Table 1. Multiple myeloma after prostate carcinoma was diagnosed.

Reference	Age	Treatment received for Prostate cancer	The duration between the occurrence of two malignancies	How was myeloma suspected	Treatment for myeloma	Remarks
[3]	73	MAB therapy	9 months	Back pain and osteolytic bone lesions progressed despite a stable, low PSA level	Melphalan and prednisolone	Expired after 33 months of diagnosis of MM
[3]	70	LHRH agonist Followed by bicalutamide	5 years	Back pain, and bone metastases with osteolytic change in the skull, ribs, and limbs	Melphalan	Expired after 8 months of diagnosis of MM
[4]	77	Radical prostatectomy Followed by leuprolide, bicalutamide, and radiotherapy	8 years	MRI bone survey showing widely metastatic disease with stable PSA	No specific therapy for MM	Asymptomatic at 20 months follow up after completion of the provided treatment
[5]	68	Radical prostatectomy plus radiotherapy	Few months	Multiple lytic cranial lesions, a crushed vertebra, and an osteolytic lesion in the humeral diaphysis	Pamidronate followed by melphalan-prednisone	NA
[6]	63	Androgen blocking therapy	3 months	Severe bone pain, hypercalcemia, and renal failure	Vincristine, adriamycin, and dexamethasone	Asymptomatic at 3 months follow up
[7]	63	Goserelin acetate, flutamide, external irradiation, bilateral orchiectomy, carboplatin, mitoxantrone, prednisone	3 years	X-rays showing multiple osteolytic lesions	Zoledronic acid, dexamethasone, thalidomide	Expired after 14 months of diagnosis of MM
[8]	67	NA	NA	Hip pain, CT images showing a lytic bone lesion	NA	NA
[14]	75	Androgen deprivation therapy was later discontinued and started on bicalutamide	NA	PET-CT for primary staging in the spine showed an equivocal lesion in the body of Th8	Radiotherapy of Th7–Th9 and subsequent chemotherapy with melphalan, prednisolone, and bortezomib	NA

MAB, maximal androgen blockade; PSA, prostate-specific antigen; MM, multiple myeloma; LHRH, Luteinizing hormone-releasing hormone; MRI, magnetic resonance imaging; NA, Not available; CT, computed tomography; PET-CT, Positron emission tomography-computed tomography; Th8, the eighth thoracic vertebra; Th7, the seventh thoracic vertebra; Th9, the ninth thoracic vertebra.

Table 2. Prostate carcinoma and multiple myeloma were diagnosed together.

Reference	Age	Findings suspicious of prostate carcinoma	Findings suspicious of multiple myeloma	Treatment	Remarks
[2]	62	PSA 122 ng/mL with back pain and radiation of pain to legs	Back pain, a skeletal survey showing lytic lesions	Vincristine, endoxan and prednisolone, melphalan, and prednisone followed by hormonal therapy	Stable at 4 months follow up
[9]	58	Hesitancy, elevated PSA (62 ng/mL)	Lower back pain, non-traumatic L3 vertebra fracture	Radiation therapy on the L3 vertebra, androgen deprivation therapy with bicalutamide, goserelin as well as bisphosphonate	Well without evidence of tumor recurrence at 37 months follow-up after diagnosis
[10]	71	MRI showing central areas of T2 hypointensity suggestive of metaphyseal sclerosis	Left thigh swelling and pain with impaired ambulation. Radiograph showing a large lytic lesion of the femur, normocytic anemia, increased serum creatinine, and elevated globulin levels	- Distal femur resection with endoprosthetic reconstruction. - Bicalutamide and leuprolide - Cyclophosphamide, bortezomib, and dexamethasone followed by autologous hematopoietic stem cell transplantation with melphalan conditioning	Stable at 2-year follow-up
[11]	83	Lower back pain and incontinence of urine	MRI showing osteolytic lesions in the skull and vertebrae.	NA	NA
[12]	70	NA	prolonged prothrombin time with lack of yellowness of plasma, the Bone scan was done at that time had revealed multiple lytic lesions	- Zoledronic acid for skeletal metastasis and anti-androgen therapy (triptorelin) - Refused multiple myeloma treatment	Expired

NA, Not available.

Table 3. Prostate carcinoma after multiple myeloma was diagnosed.

Reference	Age	Treatment received for multiple myeloma	The duration between the occurrence of two malignancies	How was prostate cancer suspected	Treatment for prostate cancer	Remarks
[13]	73	Six cycles of CDT	3 years	Extensive FDG-avid infrarenal abdominal and pelvic nodes prostate gland enlarged, lobulated with specks of calcification demonstrating diffuse, heterogeneously increased metabolic activity	Goserelin acetate hormonal treatment	No follow-up information is available
[15]	Out of a cohort of 700 consecutive patients with prostate cancer, there were four cases where multiple myeloma was diagnosed before the diagnosis of prostate cancer. Individual information on cases not available					

CDT, cyclophosphamide, dexamethasone, thalidomide; FDG, fluorodeoxyglucose.

Results

Age

Most of the patients were between the ages of 60–80 years of age. There was only one patient under the age of 60 and one patient over the age of 80, respectively. The mean age in each group, MM preceded by prostate carcinoma (69.5 years), and prostate carcinoma and MM diagnosed together (68.8 years) were similar. The age of diagnosis in patients with prostate carcinoma diagnosed after MM was available for only one patient and was 73 years.

Modality of Treatment of Prostate Cancer

In 8 cases of MM preceded by prostate carcinoma, 25% were treated with androgen deprivation therapy (ADT), the other 25% with radical prostatectomy + ADT + Chemotherapy, 12.5% with ADT, and chemotherapy, 12.5% with radical prostatectomy + radiation therapy (RT), 12.5% with ADT + RT + chemotherapy + bilateral orchiectomy and no information available on remaining 12.5%.

In 5 cases of prostate carcinoma and MM diagnosed together, 40% were treated with ADT. The remaining three 20% portions were either treated with ADT + RT + chemotherapy, or ADT + chemotherapy or no information was available on the treatment.

In 5 cases of prostate carcinoma after MM, information on treatment for prostate carcinoma is available in 1 case, which was treated with ADT.

Modality of Treatment of Multiple Myeloma

Each case of MM has been treated with different chemotherapy modalities. In the case of MM preceded by prostate carcinoma, various chemotherapy regimens tried were melphalan only, melphalan + prednisolone, pamidronate + melphalan + prednisolone, vincristine + adriamycin + dexamethasone, zoledronic acid + dexamethasone + thalidomide and melphalan + prednisolone + bortezomib. No specific treatment was provided for MM in 16.7%.

In the case of prostate carcinoma and MM diagnosed together, treatment modalities tried included vincristine + cyclophosphamide + prednisolone + melphalan, cyclophosphamide + bortezomib + dexamethasone + melphalan + autologous stem cell transplant, and resection of affected bone with endoprosthesis reconstruction. In 40% of the cases, no specific treatment was provided.

In the only case for which information is available out of 5 cases of prostate carcinoma after MM, cyclophosphamide + dexamethasone + thalidomide was used.

Diagnosis of the Second Tumor

In cases of MM preceded by prostate carcinoma, 50% were symptomatic with bone pain which led to further workup. 50% were asymptomatic and MM was diagnosed when radiological imaging as a part of the further workup for prostate carcinoma revealed osteolytic lesions.

In cases of prostate carcinoma after the initial diagnosis of MM, prostate carcinoma was diagnosed after extensive fluorodeoxyglucose (FDG) showed increased metabolic activity in infrarenal abdominal and pelvic nodes along with an enlarged prostate gland lobulated with specks of calcification.

In cases of simultaneous development of MM and prostate cancer, MM was suspected in 60% when presented with bone pain and radiology showed osteolytic lesions, 20% presenting with bone pain and non-traumatic vertebral fracture, and the remaining 20% presenting with prolonged partial thromboplastin time (PTT) with lack of yellowness of plasma with osteolytic lesions on radiological imaging. Prostate carcinoma was suspected in 50% of cases presenting with an elevated prostate-specific antigen (PSA), 25% when radiological imaging showed osteosclerosis, and 25% presenting with back pain.

The Interval of Occurrence of the Second Malignancy after Diagnosis of the First Malignancy

In cases of MM preceded by prostate carcinoma, the interval duration for the occurrence of a second tumor ranged from 3 months to 8 years, with a mean duration of 3.4 years.

In cases of prostate carcinoma after MM, 3 years was the interval duration in 1 case whose information is available.

Prognosis

In cases of MM preceded by prostate carcinoma, 40% were alive at the time of follow-up. Among 60% who expired, the interval from diagnosis of MM ranged from 8–33 months with a mean of 18 months.

In cases of prostate carcinoma and MM diagnosed together, 25% expired (unknown time after diagnosis). The remaining 75% were alive at follow-ups with a mean follow-up interval from diagnosis to 22 months. As per the above findings, MM preceded by prostate carcinoma appears to have a worse prognosis in comparison to the synchronous occurrence.

Pathogenesis of Prostate Cancer

Numerous studies have indicated that the development of prostate cancer shares a close relationship with embryonic organogenesis. It exhibits a strong reliance on androgenic hormone signaling, particularly testosterone, and there are controversial potential associations with other embryonic signaling pathways such as Sonic Hedgehog expression (Shh). Inappropriate expression of the glioma-associated oncogene homolog 1 (*GLI1*) has also been implicated in the growth and proliferation of stromal tumors [16–18]. Alternatively, peptide growth factors, including transforming growth factor β (*TGF-*β), fibroblast growth factor (*FGF*), insulin-like growth factor (*IGF*), and epidermal growth factor (*EGF*), play a role in androgen receptor (*AR*)-independent pathways [19,20]. These factors promote the proliferation of prostate epithelial cells through a process known as "crosstalk", [19], an intracellular process that occurs when the same signal is shared by more than one signaling pathway. Decreased AR activation leads to heightened sensitivity of other pathways. For instance, increased levels of IGF-1, EGF, and other growth factors subsequently activate *ERBB2* and other tyrosine receptor kinases [20], triggering the phosphatidylinositol 3-kinase (*PI3K*) pathway, specifically the *PI3K*-protein kinase B (*AKT*)-mammalian target of rapamycin (*mTOR*) pathway [21,22]. *PI3K* converts phosphatidylinositol 4,5-bisphosphonate (*PIP2*) into phosphatidylinositol 3–5-triphosphate (*PIP3*) which then recruits protein kinase B (*AKT*) proteins to the cytoplasm of luminal cells [21]. *AKT* signaling is stimulated by tuberous sclerosis 1/2 (*TSC1/2*) inhibitor of the guanosine triphosphate (*GTP*)-binding protein Ras homolog enriched in brain (*RHEB*), subsequently activating the mechanistic target of rapamycin complex 1 (*mTORC1*) kinase, a critical regulator of the cell cycle. *mTORC1* suppresses autophagy and increases prostate cancer cell proliferation [21]. *IGF-1* has been proven to activate AR-mediated gene transcription and PSA production in Lymph Node carcinoma of the prostate (*LNCaP*) cells due to this pathway [22,23]. Chen *et al*. [24] found that tumor cells can infiltrate immune cells, forming tumor-associated macrophages (*TAMs*). These *TAM*s can express PSA in aggressive forms of prostate cancer, which may contribute to the cancer's ability to spread to lymph nodes and bone tissue [25]. This suggests that the tumor microenvironment (TME) may allow alternative cell types to become malignant and boost cancer's capacity to invade other areas locally as well as systemically [25,26].

Pathogenesis of Multiple Myeloma

The exact cause of MM is not fully understood, but environmental exposures and genetic events are believed to be potential risk factors. Most MM patients initially develop from a pre-malignant stage called monoclonal gammopathy of undetermined significance (MGUS), characterized by low levels of M protein ($<$30 g/L), $<$10% of abnormal plasma cells in the bone marrow, and lack of MM-related symptoms [27]. Several genetic changes, signaling pathways, and alterations of the tumor microenvironment are important for the pathogenesis of MM. Chromosomal translocations, genetic mutations, epigenetic modifications, and aneuploidy (abnormal chromosome number), are all important factors in the development and flourishment of the disease [1]. The initiating events are thought to occur in the germinal center during the process of class switching and somatic hypermutation [28]. Translocations often involve the immunoglobulin heavy chain (*IGH*) gene loci and specific partner genes. The majority of translocations are associated with the *IGH* chain locus at chromosome 14, leading to the activation of oncogenes regulated by the *IGH* enhancer. For example, the *t(11;14)* translocation is linked to cyclin D1 (*CCND1*) overexpression, which encodes cyclin D1 and plays a vital role in cell cycle progression [29]. The *t(4;14)* translocation, found in 10 to 15% of MM patients, results in increased expression of fibroblast growth factor receptor 3 (*FGFR3*) and nuclear receptor-binding SET domain protein 2 (*NSD2*) [30,31]. Other usual translocations include *t(14;16)* involving minor allele frequency (*MAF*), *t(14;20)* involving V-maf musculoaponeurotic fibrosarcoma oncogene homolog B (*MAFB*), and *t(6;14)* involving cyclin D3 (*CCND3*) [32–36]. Aneuploidy, including hyperdiploidy, pseudodiploidy and hypodiploidy is another possible driving factor. These genetic abnormalities influence numerous signaling pathways, such as the nuclear factor kappa B (*NF-*κ*B*) pathway, the mitogen-activated protein kinase (*MAPK*) pathway, and the cell cycle pathway. The *t(4;14)* translocation leads to *FGFR3* overexpression and activation of the signaling cascade. Mutations

in *RAS* genes (*NRAS* and *KRAS*) disrupt the *MAPK* pathway in MM [37]. These activating mutations in *MAPK* signaling are associated with aggressive forms of myeloma. Both the cellular and noncellular components of the BMME contribute to the formation of a tumor-promoting environment. Bone marrow stromal cells (BMSCs) are essential for the growth of MM cells. The interaction between MM cells and the BMME leads to the secretion of various cytokines and growth factors, including interleukin-6 (*IL-6*), insulin-like growth factor (*IGF-1*), B-cell activating factor (*BAFF*), a proliferation-inducing ligand (*APRIL*), tumor necrosis factor-alpha (*TNF-*α) and vascular endothelial growth factor (*VEGF*) [38]. These soluble factors activate intracellular signals that regulate the growth, proliferation, migration, and drug resistance of malignant cells [39].

Possible Link between Prostate Carcinoma and Multiple Myeloma

Coexisting malignancies are being more frequently identified and studied. Synchronized occurrence can be either due to common triggering factors or can be merely coincidental. Malignant neoplasms, occurring either synchronous or metachronous, may be linked to genetic, environmental, and occupational factors. Infections such as Epstein-Barr virus and Helicobacter pylori, immunodeficiency (causing impaired T-cell function and inadequate suppression of B cells by T cells), and exposure to ultraviolet radiation are also associated with the development of MM. Additionally, patients who have undergone radiation therapy or chemotherapy may be at higher risk [7]. Chronic antigenic stimulation resulting from infections or other chronic diseases, as well as exposure to specific toxic substances or radiation have been identified as factors that increase the incidence of MM [7].

The incidence of the concurrent occurrence of prostate cancer and hematolymphoid malignancies is 1.2% [40]. In a study conducted by Kao *et al.* [15], it was found that out of 700 consecutive patients with prostate cancer, 4 cases of MM preceded the diagnosis of prostate cancer. This figure was significantly higher than the expected 0.028 cases of MM among 700 patients with prostate cancer, which is equal to 4 per 100,000 people as per the general population [15]. Further research has shown that individuals with a family history of other types of tumors, especially those in the prostate or brain, had an increased risk of MM [41,42]. Additionally, studies that have sought to investigate the relationship between MM and prostate cancer have suggested that certain hereditary cancer syndromes and familial MM might predispose individuals to develop both hematologic malignancies and a second solid tumor, such as prostate cancer [41–44]. It has been hypothesized that the similarity in stimulatory mechanisms, pathways, and tumor microenvironments between prostate cancer and multiple myeloma (MM) may be the cause of their association. Linkage analysis of hereditary prostate cancer has revealed several candidate genes located on chromosomes 1, X, and 17 [15]. Furthermore, as mentioned above, chromosomal translocations in MM usually involve the immunoglobulin heavy chain (*IGH*) on chromosome *14q32* and are associated with 5 major oncogenes: cyclin D1 *(11q13)*, cyclin D3 *(6p21)*, *C-MAF (16q23.1)*, *FGFR3 (4p16.3)*, and *MAFB (20q11)* [45]. Additionally, karyotypes of MM are complex and have more similarity to those of epithelial cells and the blast phase of chronic myelogenous leukemia (CML) [45].

In addition to genetic events, research has demonstrated that the BMME of both prostate cancer and MM share important similarities. Certain cytokines and growth factors play a role in the neoplastic transformation and clinical progression of both diseases [15]. Chemokines secreted from MM cells including *IL-6*, *IGF-1*, stromal cell-derived factor-1 (*SDF-1*), and vascular endothelial growth factor (*VEGF*) (mediator of angiogenesis) [46],can lead to immunosuppression which can cause the progression of prostate adenocarcinoma. A study has shown an elevated risk of prostate cancer in individuals with higher levels of *IGF-1* (relative risk 4.3 in the highest quartile of plasma *IGF-1* in comparison to the lowest quartile), suggesting a potential link between elevated *IGF-1* concentrations and prostate cancer development [15]. *SDF-1* has recently been identified as a chemoattractant for metastatic prostate carcinoma cells to the bone, and its dysregulation may contribute to the progression of prostate cancer by impairing immune responses [2]. *c-MYC* dysregulation is observed in a significant proportion (45–90%) of advanced myeloma cells, and *c-MYC* amplification is associated with a worse prognosis in prostate cancer patients [2]. Immune dysfunctions caused by MM may lead to the accelerated progression of latent or clinically insignificant prostate cancers, resulting in a more aggressive phenotype with increased prostate-specific antigen (PSA) levels or palpable masses. *IL-6* and *IGF-1* have been implicated in activating the *MAPK* pathway which suppresses apoptosis in prostate adenocarcinoma [15]. In a recent study, Kristinsson *et al.* [47], were unable to re-affirm the potential risk of prostate cancer in patients with monoclonal gammopathy of undetermined significance (MGUS), a precursor to MM which had been determined in their earlier research [15].

The *t(14;16)* chromosomal translocation in MM and the homozygous deletion in adenocarcinomas such as breast and prostate cancers are either located nearby or associated with fragile site fos-related antigen (*FRA*) *16D (16q23.2)*. In these cases, DNA instability and altered gene expression with the loss of heterozygosity are frequently observed within these regions [48,49]. The relatively new techniques like DNA microarrays, proteomic pattern analysis, and comparative genomic hybridization offer potential avenues to uncover additional connections between prostate cancer and MM [50,51]. These methods enable researchers to explore the molecular profiles and genetic alterations associated with both diseases. Furthermore, the use of cyto-

static and radiation therapies in cancer treatment may contribute to the development of second cancers, either independently or in combination with other factors. In a case study of a patient with testicular plasmacytoma following chemical castration for prostate cancer, Kahr *et al*. [52] suggested that surgical stress could have exacerbated the clinical course of myeloma, likely due to increased levels of *IL-6* after surgery, which could stimulate myeloma growth. This also raises another question, if the castration treatment (chemical, as well as surgical) for prostate cancer, increases the risk of myeloma. Upon analysis of 7 cases of prostate cancer which later developed into MM, all of them had received either chemical or surgical castration therapy [3–8]. Further studies are imperative to confirm these hypotheses. In a case study of a patient with testicular plasmacytoma following chemical castration for prostate cancer, it was suggested that surgical stress could have exacerbated the clinical course of myeloma, possibly due to increased levels of *IL-6* after surgery, which could stimulate myeloma growth. This raises the question of whether castration treatments (chemical or surgical) for prostate cancer could increase the risk of developing myeloma. Analysis of seven cases of prostate cancer progressing to MM revealed that all patients had undergone chemical or surgical castration therapy. However, further studies are necessary to validate these hypotheses and explore the potential link between castration therapy for prostate cancer and the risk of myeloma development.

Conclusions

Prostate carcinoma and MM can occur, either synchronously or sequentially. There is a possibility that the two pathologies may be associated based on their presence together. The pathogenesis of this co-existence is yet to be analyzed. Awareness of the possible interconnection between MM and prostate carcinoma is necessary so that appropriate treatment can be administered.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

Author Contributions

AP wrote the manuscript, searched for the literature and acquired the data; OH, LE, RN, UM, and RW acquired the data; JCW mentored the writing, constructed the idea. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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