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A Case Report of Putative Autoimmunity to Prostate Cancer after Immune-Mediated Rejection of Melanoma via a Shared Tumor Antigen

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INTRODUCTION

Patients with metastatic melanoma or castration-resistant metastatic prostate cancer have limited life expectancy. We report the case of a patient with metastatic melanoma who was free of disease progression for 18 years and whose prostate cancer, diagnosed 14 years after his melanoma diagnosis, entered spontaneous (though transient) remission. We found that the patient produced antibodies and T cells specific for prostate-specific membrane antigen (PSMA), suggesting that he developed auto-immunity to prostate cancer after immune-mediated rejection of the melanoma. We propose that an immune response to a shared tumor antigen resulted in long-lasting anti-tumor effects against both malignancies.

CASE REPORT

A 93-year-old man presented with metastatic melanoma diagnosed 23 years earlier. He had undergone a wide excision of the 2.5-mm primary tumor in his lower back and lymph node dissection, which revealed one positive node. The following year, the patient received an experimental immune therapy in the adjuvant setting that targeted anti-proteoglycan antibody. Over the next four years, he underwent multiple metastasectomies, including resection of a metastasis to the brain, multiple bowel resections, and right axillary lymphadenectomy. He also received a single dose of dacarbazine. Since his last surgery 18 years ago, there has been no recurrence and he has no evidence of disease.

Fourteen years after presenting with melanoma, the patient was found to have a PSA level of 700 ng/mL, and subsequent biopsy confirmed Gleason 7 (3+4) prostate adenocarcinoma. Bone scintigraphy demonstrated multiple metastases in the axial skeleton. The patient began hormonal therapy with bicalutamide and leuprolide. He achieved a PSA nadir of 0.9 ng/mL

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over the next 7 months, after which his PSA began to rise. Bicalutamide was withdrawn approximately 8 months after being initiated, when his PSA reached 25 without a subsequent PSA decline. Leuprolide was continued throughout his treatment course. As shown in Figure 1, when his PSA reached 61, a 2-month trial of high-dose ketoconazole with hydrocortisone was started, again without an apparent favorable impact on his PSA. However, one month after discontinuation of ketoconazole (and four months after discontinuing bicalutamide), the patient's PSA declined, reaching a nadir of 0.08 more than four months after ketoconazole was stopped. Bone scans performed three and eight months after ketoconazole was stopped also showed dramatic improvement in existing lesions (Figure 2). The patient maintained no evidence of disease recurrence for 9.8 months after discontinuing ketoconazole, when his PSA again began to rise and new bone lesions were revealed on bone scintigraphy. When his PSA reached a level of 36 (17 months after ketoconazole was discontinued), he was unsuccessfully treated with a variety of drugs and biologics, including trastuzumab, geldanamycin, and everolimus with gefitinib, on clinical trials. Docetaxel was started when the patient's PSA reached 324 (every 3 weeks for 4 cycles, with a delay after cycle 2 in order to receive palliative radiation to the pelvis), achieving a PSA nadir of 24.36. Following a 6.6-month treatment break, docetaxel was restarted at a PSA of 139 for another 3 cycles, achieving a PSA nadir of 20. Following a 5-month break the patient's PSA was 72; he was treated with docetaxel every 3 weeks for another 4 cycles and received a dose of samarium 153 on a clinical trial. He once again experienced a rapid PSA decline to a new nadir of 1.32, and PSA was maintained below 2.5 for 6 months, at which point it began to rise. He did not require additional therapy for 12 months. The patient received another two doses of docetaxel and then decided to change treatment to supportive care. He had received 11 doses of chemotherapy over 40 months and lived over 65 months after starting chemotherapy for prostate cancer. After living with castration-resistant metastatic disease for 9 years, the patient died of prostate cancer at the age of 93.

IMMUNE RECOGNITION OF PSMA

Patient sera were evaluated for antibodies specific to PSMA protein by ELISA (Figure 3). Over a 2-year period beginning with his remission after androgen blockade and ending during docetaxel treatment, 3 independent samples of his serum were found to contain human immunoglobulin G (IgG) that bound to recombinant PSMA protein. In an ELISA using 113 individual peptides derived from PSMA, where each peptide was 18–20 residues in length, and overlapped by 12 residues, we confirmed binding to a PSMA peptide spanning residues 430 to 449. Because CD4⁺ T cells are required for antibody production, we anticipated that the patient would also have PSMA-specific CD4⁺ T cells. Peripheral blood mononuclear cells (PBMCs) were obtained after a single leukapheresis and Ficoll-mediated (GE Healthcare, Piscataway, NJ) density centrifugation at month 54, and they were stored in liquid N₂. Repeated blood draws were avoided. A library of 113 overlapping peptides, 18-20 residues in length with a 12-residue overlap, was synthesized from the PSMA primary sequence. Four pools of 28-29 peptides were prepared and used to stimulate patient PBMCs in vitro for 10 days. Recognition of peptides was determined by measuring the level of the activation marker INF- γ by CD3+CD4⁺ T cells in the presence and absence of peptide by intracellular cytokine assay (ICCA).[1] Positive cultures were re-stimulated with sub-pools containing 3-5 peptides and then with individual peptides. In this way, we identified four PSMA peptides recognized by CD4⁺ T cells (Figure 3). These are AHYDVLLSYPNKTHPNYISI (111-130); KVKMHIHSTNEVTRIYNV (340-358); YSLVHNLTKELKSPDEGF (471-488) and LVEKFYDPMFKYHLTVAQV (561-579). Peptides 340-358 and 561-579 overlap in part with peptides shown to bind CD4 T cells in prostate cancer patients.[2]

DISCUSSION

This patient is unique in that he had melanoma that had metastasized to the brain and mesentery and was free of disease 23 years after diagnosis and treatment. In addition, he developed castration-resistant metastatic prostate cancer characterized by a spontaneous remission after treatment with leuprolide and ketoconazole (there is no known ketoconazole withdrawal response), with re-inducible periods of prolonged remission after short courses of cytotoxic treatment. We sought an immune mechanism that might account for and link these phenomena. We hypothesized that the patient mounted a unique immune-mediated response directed against a tumor antigen shared between the two separate malignancies.

PSMA, a cell surface protein that was first characterized in prostate cancer, has been shown to be expressed by the neovasculature endothelium of many solid tumors, including melanoma.[3] We demonstrated the presence of PSMA-specific CD4⁺ T cells and PSMA-specific antibodies in the patient's blood. In the absence of active immunization with PSMA protein, we propose that his prostate tumor regression resulted from a reactivation of his immune system after initial activation by PSMA expressed in the neovasculature of his melanoma tumor.

Future studies on immunomodulatory therapies may benefit from studying patients who are able to harness the remarkable abilities of their immune system to elicit complete tumor rejection. Specifically, we hypothesize that this patient's immune system was primed to PSMA expressed by the melanoma malignancy and launched an IgG and/or T cell-mediated response, preventing further tumor progression despite the brevity of interventional treatment. Further, it seems that the patient's immunologic memory was reactivated more than a decade later when he developed prostate cancer, exposing his immune system to PSMA again. This reactivation may have been amplified by the androgen blockade and cytotoxic treatments used to treat the prostate cancer. Serum antibodies were detected as early as month 23, during a period of spontaneous remission following androgen blockade. Samples were not available prior to that date. Agents that cause cell death can promote antigen presentation to the immune system and amplification of long-lived memory T and memory B cells.[4,5] Androgen ablation has been shown to induce CD4⁺ T cell infiltrates in human prostate cancer.[6] In essence, we suggest that our patient became auto-immunized against prostate cancer by surviving melanoma, and that androgen ablation and/or chemotherapy may have expanded the immune response.

Melanoma is believed by most to be an immunogenic malignancy.[7] Cases of spontaneous regressions are often attributed to patients developing unique immune responses against tumor-specific antigens.[8] Past studies have established the variability of antigens expressed by melanoma cells, many of which are unique to the individual patient. However, this is the first report in which PSMA has been found as a target of antibodies and T cells in a patient experiencing long-term survival from either melanoma or prostate cancer.

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CLINICAL PRACTICE POINTS

- Although prostate-specific membrane antigen (PSMA) is known to be expressed in localized and metastatic prostate cancer—with the greatest expression seen in patients with castration-resistant metastatic disease—it is also expressed in the neovasculature of non-prostate solid tumors.
- A patient with a history of metastatic melanoma, which did not recur following several metastasectomies, developed metastatic prostate cancer and experienced an apparent spontaneous remission. Immune studies revealed that the patient produced antibodies and T cells specific for prostate-specific membrane antigen (PSMA), suggesting that he developed auto-immunity to prostate cancer after immune-mediated rejection of the melanoma.
- To our knowledge, this is the first report in which prior exposure to PSMA via a metastatic non-prostate solid tumor appears to have resulted in auto-immunity to prostate cancer. We believe this is also the first report of PSMA that is expressed in the neovasculature of a previous cancer impacting clinical outcome when PSMA is expressed on the metastases of a second cancer.
- These findings suggest that PSMA-directed immune strategies have the potential to alter the clinical course of prostate cancer. Inducing T cell-mediated immunity with anti-PSMA immunologic memory (in the absence of an antecedent non-prostate solid tumor) would be highly desirable as an anti-prostate cancer strategy.

Figure 1.

Plots showing prostate-specific antigen (PSA) levels while undergoing hormonal treatment and cytotoxic and radiopharmaceutical treatment. Following a reduction in PSA while receiving leuprolide and bicalutamide at diagnosis (not shown), the patient's PSA began to rise. His PSA continued to rise despite anti-androgen withdrawal followed by ketoconazole, as shown. After discontinuing ketoconazole, his PSA spontaneously declined and did not rise for 9.8 months. Serum was drawn for enzyme-linked immunosorbent assay (ELISA) 3 times, in the intervals as shown, and an apheresis performed between the 6th and 7th doses of docetaxel. Durable episodes of freedom from progression in this context are unusual, and prompted a search for a mechanism linking his unusual course of metastatic melanoma with that of his metastatic prostate cancer. Another PSA decline was seen after treatment with docetaxel and ¹⁵³Sm. The patient remained on leuprolide during the treatment course, and testosterone remained at castrate levels.

Figure 2.
Bone scan improvement 1 month, 3 months, and 8 months after discontinuing ketoconazole (left to right).

Figure 3. Serum immunoglobulin and T cell responses to PSMA

3a. Enzyme-linked immunosorbent assay (ELISA). Purified PSMA protein was used to coat EIA/RIA plates (Costar, Corning, NY), and after blocking with 5% non-fat dry milk, serum from the study patient drawn at month 23, 35, or 48, or from pooled normal human subjects (NHS), was diluted 1/100 in phosphate-buffered saline (PBS) and incubated overnight at 4°C. PBS served as an additional control. Plates were washed with PBS and a non-ionic detergent (0.1% Tween 20 [Sigma-Aldrich, St Louis, MO]) three times and then with PBS three times, and incubated with alkaline phosphatase (AP)-conjugated goat anti-human IgG (all isotypes) (Southern Biotech, Birmingham, AL, catalog #2040-04, 1:2000). Color development was accomplished by addition of AttoPhos reagents (Fisher Scientific, Pittsburgh, PA).

3b,c. Intracellular cytokine assay (ICCA). PBMCs from an apheresis performed during month 54 were cultured for 10 days in RPMI 1640 + 10% fetal calf serum + IL-2 (10 IU/mL) and IL-15 10 (ng/mL) in the presence of one of four pools of 28-29 peptides from PSMA (pool #1). All cultures were performed in triplicate. After 10 days, cells in each well were divided into two cultures, one cultured with the original peptides and one without. After 1 hour, brefeldin (5µM) was added to all cultures to prevent cytokine release. Cells were cultured overnight and then stained for the surface markers CD3, CD4, CD8, and the intracellular marker INF-γ and analyzed by flow cytometry on a BD LSR (Becton, Dickinson, Franklin Lakes, NJ). Cultures in which CD3+ CD4+ cells produced at least 2-fold more INF-γ in the presence of peptide compared to cultures without peptide were considered positive and were reconfirmed. Cells were also stimulated with small peptide subpools until a single peptide was identified as the target.

3c. Pools 16-20 and 3-28 are fully contained within the original pool#1, and both contained peptide 18, AHYDVLLSYPNKTHPNYISI (111-130). When this was retested, it was found to be the dominant epitope.