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CASE REPORT

Melanoma of Non-Sun Exposed Skin in a Man with Previous Prostate Cancer: Recognition of a Recently Confirmed Association

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ABSTRACT

Background: The association of an increased risk to develop melanoma in patients with prostate cancer has recently been confirmed.

Purpose: The postulated etiologic relationship between prostate cancer and the subsequent occurrence of melanoma is discussed.

Methods: A man with previous prostate cancer who developed melanoma on the plantar surface of his left great toe is described and the possibility of high levels of endogenous androgens promoting not only prostate cancer, but also increased risk of melanoma are reviewed.

Results: Modification of the host immune response, alteration of chromosome telomere length, and/or imbalance of androgen level (presenting as severe teenage acne) are potential mechanisms whereby high levels of endogenous androgens may contribute to the association between prostate cancer and risk of melanoma.

Conclusions: An increased surveillance for melanoma should be considered in prostate cancer patients. Complete skin examination in men who have had prostate cancer—especially in those individuals diagnosed with prostate cancer prior to age 68 years—should regularly be performed.

Keywords: Acne; Adenocarcinoma; Androgen; Carcinoma; Dermatology; Malignant; Melanoma; Prostate; Telomerase; Telomere

INTRODUCTION

Melanoma is the fifth most commonly diagnosed cancer among men in the United States and may, in part, be etiologically associated with androgen levels or androgen receptors in the tumor or both [1–6]. Prostate cancer is an androgen-related malignancy [7–11]. The statistically significant development of malignant melanoma in prostate cancer patients has recently been confirmed [12]. A man with previous prostate cancer who developed melanoma on the plantar surface of his left

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great toe is described and the postulated etiologic relationship between prostate cancer and the subsequent occurrence of melanoma is discussed.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 and 2008. Informed consent was obtained from all patients for being included in the study.

CASE REPORT

A 59-year-old Caucasian male presented with asymptomatic black discoloration of his left big toe. At least 5 years earlier, he had originally noted some dark spots on the undersurface of his toe. Recently, in November 2013, he was prompted to seek medical attention since he thought new fainter spots had appeared which looked like a bruise, but were irregular in shape and colored.

As a teenager, he had acne. He had been treated with various topical preparations. In addition, during high school, he received oral tetracycline for at least 3 years.

His past medical history was also remarkable for adenocarcinoma of the prostate, diagnosed at age 51 years. He had mild lower urinary tract symptoms in late 2004; in April 2005 he had an abnormal digital rectal examination of his prostate and his prostate-specific antigen was elevated at 7.1 ng/ml. In May 2005, he underwent a trans-rectal biopsy of his prostate that showed a Gleason score of $4 + 3$ with bilateral involvement.

Treatment was initiated with bicalutamide (Casodex®, Astrazeneca, Delaware, USA) 50 mg daily. His prostate-specific antigen dropped to 0.3 ng/ml by July 2005. Seven months later, in December 2005, leuprolide (Lupron Depot®, AbbVie Inc., Chicago, USA) injections, every 3 months, were added.

A magnetic resonance imaging (MRI) study in January 2006 showed extension of the tumor outside the prostate into the seminal vesicles and surrounding tissues (stage T3b radiographically). From March 2006 to May 2006, he was treated with external beam radiation. He continued to receive androgen deprivation therapy for approximately 2 years. The last leuprolide injection was in December 2006 and he stopped using bicalutamide in March 2007. His prostate-specific antigen continues to remain below 0.4 ng/ml.

Examination of the plantar surface of his left big toe showed three areas of black-brown hyperpigmentation (Fig. 1). Each patch had fading, irregular-shaped borders. The proximal macule was 15 × 12 mm with a lighter proximal area and a darker distal area; both areas were biopsied and each showed melanoma in situ. In addition, the distal dark macule (5 × 5 mm and closer to the tip of the toe) and the lateral dark macule (6 × 4 mm and near the second toe)

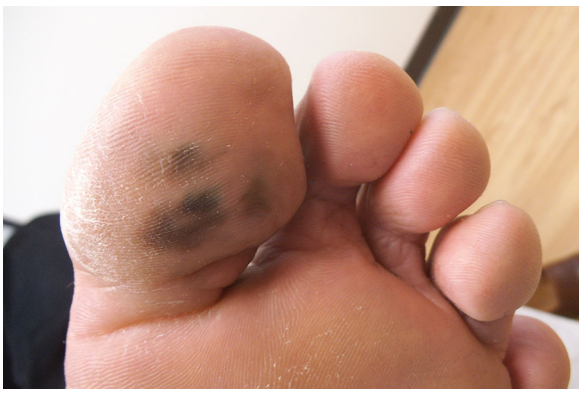

Fig. 1 Three patches of black-brown hyperpigmentation with fading irregular-shaped borders are present on the plantar surface of the left big toe. Biopsies from the proximal lighter area and the distal darker area of the larger patch closest to the foot both showed melanoma in situ. All three of the pigmented patches, in addition to 5 mm of normal-appearing adjacent skin, were excised

were also biopsied; microscopic examination showed melanocytic hyperplasia and atypical intraepidermal melanocytic proliferation, respectively. With regard to management, treatment of the latter diagnosis is similar to that of melanoma in situ.

Complete excision of all three black-brown patches, including an additional 5 mm margin of normal-appearing skin, was performed and the wound was covered with a full-thickness skin graft.

DISCUSSION

Carcinoma of the prostate is the most common non-cutaneous cancer in the United States [2]. Earlier epidemiology studies have observed an increase in melanoma in men with a history of prostate cancer [13, 14]. Recently, Li et al. prospectively examined this issue and confirmed the association between a personal history of prostate cancer and an increased risk of subsequent melanoma in white men [12, 15, 16].

High levels of endogenous androgens have been postulated to contribute to the association between prostate cancer and risk of melanoma. Possible androgen-associated mechanisms of pathogenesis have been hypothesized. Some of these include host immune response modification, chromosome telomere length alteration, and androgen level imbalance [9–11].

A compromised immune response may affect the individual's risk of developing melanoma. Indeed, the host's immune response can be suppressed by androgens, promoting tumorigenesis of not only prostate cancer but also melanoma. In contrast, immunotherapy is a potential therapeutic intervention for prostate cancer and a patient's response to melanoma vaccine and survival can both be improved after their immune status has been enhanced following a blocking or elimination of androgen signaling [17–21].

Telomeres are the tiny bits of DNA that cap the ends of chromosomes [22]. They prevent chromosomes from unraveling and fusing with each other. Telomeres shorten not only as people age but also each time a cell divides; eventually, the cell dies when the telomere becomes too short [22, 23]. However, an increased risk of melanoma has been associated with long telomeres [24].

Telomerase is an anti-aging enzyme [22, 23]. It protects telomeres from wearing down and rebuilds them. Androgen exposure in vitro has been demonstrated to stimulate telomerase activity resulting in elongation of telomeres and extension of melanocyte life span [25]. Hence, by increasing telomere DNA replication and subsequent telomere length, androgens may influence the risk of melanoma development [26, 27].

Androgen imbalance may be an integral component in the tumorigenesis of not only prostate cancer, but also the enhanced susceptibility to develop melanoma. An early clinical manifestation of androgen imbalance is acne [28]. Patients with severe acne, defined by use of tetracycline for four or more years, have an increased risk of prostate cancer [28, 29]. Li et al. [12] also observed a significant positive association between severe teenage acne and melanoma risk.

The patient in this report had moderate to severe acne as a teenager which may represent an early indication of androgen imbalance. He received tetracycline for at least 3 years when he was in high school. He developed prostate cancer at the age of 51 years. Subsequently, he developed melanoma in situ on the sun protected plantar left big toe. Similar to this

man, Li et al. [12] also observed a higher hazard ratio of melanoma among patients with prostate cancer whose median age at diagnosis was less than or equal to 68 years.

CONCLUSION

The association of an increased risk of developing melanoma in patients with prostate cancer has recently been confirmed. Prostate cancer is an androgen-related malignancy and high levels of endogenous androgens, possibly resulting in modification of the host immune response, alteration of chromosome telomere length, and/or imbalance of androgen level (presenting as severe teenage acne). This may contribute to the association between prostate cancer and risk of melanoma. It may be warranted to regularly perform complete skin examination in men who have had prostate cancer, especially in those individuals diagnosed with prostate cancer prior to age 68 years.

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REFERENCES

1. Ingraffea A. Melanoma. Facial Plast Surg Clin North Am. 2013;21:33–42.
2. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin. 2013;63:11–30.
3. Morvillo V, Luthy IA, Bravo AI, Capurro MI, Portela P, Calandra RS, Mordoh J. Androgen receptors in human melanoma cell lines IIB-MEL-LES and IIB-MEL-IAN and in human melanoma metastases. Melanoma Res. 2002;12:529–38.
4. Slominski A, Tobin DJ, Shibahara S, Wortsman J. Melanin pigmentation in mammalian skin and its hormonal regulation. Physiol Rev. 2004;84:1156–228.
5. Rumke P, Persijn JP, Korsten CB. Oestrogen and androgen receptors in melanoma. Br J Cancer. 1980;41:652–6.
6. Rampen FHJ, Mulder JH. Malignant melanoma: an androgen-dependent tumour? Lancet. 1980;1:562–5.
7. Bosland MC, Mahmoud AM. Hormones and prostate carcinogenesis: androgens and estrogens. J Carcinog. 2011;10:33.
8. Bosland MC. Sex steroids and prostate carcinogenesis: integrated, multifactorial working hypothesis. Ann NY Acad Sci. 2006;1089:168–76.
9. Hyde Z, Flicker L, McCaul KA, Almeida OP, Hankey GJ, Chubb SAP, Yeap BB. Associations between testosterone levels and incident prostate, lung, and colorectal cancer. A population-based study. Cancer Epidemiol Biomarkers Prev. 2012;21:1319–29.

10. Bosland MC. The role of steroid hormones in prostate carcinogenesis (Chapter 2). J Natl Cancer Inst Monogr. 2000;27:39–66.

11. Gann PH, Hennekens CH, Ma J, Christopher L, Stampfer MJ. Prospective study of sex hormone levels and risk of prostate cancer. J Natl Cancer Inst. 1996;88:1118–26.

12. Li W-Q, Qureshi AA, Ma J, Goldstein AM, Giovannucci EL, Stampfer MJ, Han J. Personal history of prostate cancer and increased risk of incident melanoma in the United States. J Clin Oncol. 2013;31:4394–9.

13. Yang GB, Barnholtz-Sloan JS, Chen Y, Bordeaux JS. Risk and survival of cutaneous melanoma diagnosed subsequent to a previous cancer. Arch Dermatol. 2011;147:1395–402.

14. Braisch U, Meyer M, Radespiel-Troger M. Risk of subsequent primary cancer among prostate cancer patients in Bavaria, Germany. Eur J Cancer Prev. 2012;21:552–9.

15. Giovannucci E, Rimm EB, Colditz GA, Stampfer MJ, Ascherio A, Chute CG, Willett WC. A prospective study of dietary fat and risk of prostate cancer. J Natl Cancer Inst. 1993;85:1571–9.

16. Steering Committee of the Physicians' Health Study Research Group. Final report on the aspirin component of the ongoing Physicians' Health Study. N Engl J Med. 1989;321:129–35.

17. Cha E, Fong L. Immunotherapy for prostate cancer: biology and therapeutic approaches. J Clin Oncol. 2011;29:3677–85.

18. Hsueh EC, Gupta RK, Lefor A, Reyzin G, Ye W, Morton DL. Androgen blockade enhances response to melanoma vaccine. J Surg Res. 2003;110:393–8.

19. Kwek SS, Cha E, Fong L. Unmasking the immune recognition of prostate cancer with CTLA4 blockade. Nat Rev Cancer. 2012;12:289–97.

20. Drake CG, Lipson EJ, Brahmer JR. Breathing new life into immunotherapy: review of melanoma, lung and kidney cancer. Nat Rev Clin Oncol. 2014;11:24–37.

21. Raaijmakers MI, Rozati S, Goldinger SM, Widmer DS, Dummer R, Levesque MP. Melanoma immunotherapy: historical precedents, recent successes and future prospects. Immunotherapy. 2013;5:169–82.

22. Cohen PR: Telomeres and telomerase: Can a topical telomerase activator reverse cutaneous aging? Cutis blog; 2013. http://www.cutis.com/the-publication/the-roundup-blog/article/telomeres-and-telomerase-can-a-topical-telomerase-activator-reverse-cutaneous-aging/8a3a0c17f111301a92fe5517a9e7a842.html. Last access Feb 11, 2014.

23. Lunau K. How long will you live? Maclean's Mag. 2013;126(19, 20):65–8.

24. Nan H, Du M, DeVivo I, Manson JE, Liu S, McTiernan A, Curb JD, Lessin LS, Bonner MR, Guo Q, Qureshi AA, Hunter DJ, Han J. Shorter telomeres associated with a reduced risk of melanoma development. Cancer Res. 2011;71:6758–63.

25. Calado RT, Yewdell WT, Wilkerson KL, Regal JA, Kajigaya S, Stratakis CA, Young NS. Sex hormones, acting on the TERT gene, increase telomerase activity in human primary hematopoietic cells. Blood. 2009;114:2236–43.

26. Zhou J, Richardson M, Reddy V, Menon M, Barrack ER, Reddy GP-V, Kim S-H. Structural and functional association of androgen receptor with telomeres in prostate cancer cells. Aging. 2013;5:3–17.

27. Kim S-H, Richardson M, Chinnakannu K, Bai VU, Menon M, Barrack ER, Reddy GP-V. Androgen receptor interacts with telomeric proteins in prostate cancer cells. J Biol Chem. 2010;285:10472–6.

28. Williams HC, Dellavalle RP, Garner S. Acne vulgaris. Lancet. 2012;379:361–72.

29. Sutcliffe S, Giovannucci E, Isaacs WB, Willett WC, Platz EA. Acne and risk of prostate cancer. Int J Cancer. 2007;121:2688–92.