Cancer Immunoprevention: A Case Report Raising the Possibility of "Immuno-interception"

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ABSTRACT

Immune checkpoint blockade therapy provides substantial benefits for subsets of patients with advanced cancer, but its utility for cancer prevention is unknown. Lynch syndrome (MIM 120435) is characterized by defective DNA mismatch repair and predisposition to multiple cancers. A variant of Lynch syndrome, Muir–Torre syndrome (MIM 158320), is characterized by frequent gastrointestinal tumors and hyperplastic or neoplastic skin tumors. We report the case of a man with Muir–Torre syndrome who had 136 cutaneous or visceral hyperplastic or neoplastic lesions over a period of 19 years (mean 7.5 neoplasms/year, range 2–26) prior to receiving pembrolizumab immunotherapy as part of multimodality treatment for invasive bladder cancer. He not only had a complete response of the bladder cancer, but also was noted to have an absence of new cancers during a 22-month follow-up period. This case adds to the rationale for exploring the utility of immune checkpoint blockade for cancer prevention, particularly for patients with DNA repair deficits.

Introduction

The clinically demonstrated utility of antiviral vaccines to reduce risk of virally initiated cancers represents a major success in cancer immunoprevention. There is interest in the possibility that immunoprevention may also be useful where viral carcinogenesis does not play a major role (1–6).

Therapies that target immune checkpoints lead to impressive clinical improvements in subsets of patients with advanced cancer (7), but the hypothesis that these therapies can be used to reduce cancer risk has not been fully explored.

Muir and colleagues (8) and Torre (9) independently described a syndrome of cutaneous neoplasms associated with increased risk of visceral cancers. This was later recognized as a variant of Lynch syndrome, caused by germline pathogenic variants in mismatch repair genes, resulting in a "mutator phenotype" associated with >12 mutations/10^6 bases (6, 10).

It is recognized that cancers with a high-mutational burden respond better to immune checkpoint blockade than those with low-mutational burden (11). Therefore, as expected, cancers with mismatch repair deficiency tend to respond well to these treatments (12, 13).

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There is an obvious clinical need to reduce cancer incidence in patients with DNA repair deficits, and prophylactic surgery is commonly employed. Clinical trials designed to evaluate strategies to reduce cancer incidence are challenging: in populations where baseline risk is low, a large number of subjects and long follow-up periods are required. On the other hand, studies of interventions for patients with syndromes associated with greatly increased risk are logistically challenging because individual cases are rare and geographically dispersed.

We provide here an "$n = 1$" case report of a man with Muir–Torre syndrome consistent with the possibility that immune checkpoint blockade is useful for cancer prevention.

Materials and Methods

Following informed consent, and with anonymization conforming to policies of local institutional review board, we reviewed the entire available medical history of a patient with Muir–Torre syndrome who had received immunotherapy with pembrolizumab for treatment of invasive bladder cancer. Molecular diagnosis was obtained by protein truncation test and sequencing as described below (14).

Results

Case report

The patient is a 64-year-old male of Egyptian origin. His mother had a history of multiple neoplasms, but her clinical details are unavailable and genetic testing was not performed. He was first referred to our clinic in 2005, and we were able to obtain detailed medical records dating back to February 1999.

In view of his personal and family history of multiple neoplasms, leukocyte RNA was analyzed for a mutation in the *MSH2* and *MLH1* genes using the protein truncation test. A

Table 1. List of new hyperplastic or neoplastic lesions detected during the period of detailed observation.

Date (MM-DD-YYYY)	Diagnosis	Site	Treatment
02-16-1999	Sebaceous epithelioma	Skin; scrotum	Excision
		Skin; groin	Excision
09-14-1999	Squamous cell carcinoma, well-differentiated	Skin; right thigh	Excision
10-26-1999	Sebaceous epithelioma	Skin; right thorax	Excision
10-22-1999	Hyperplastic polyps	Colon	Polypectomy
01-17-2000	Sebaceous hyperplasia	Skin; left temple	Excision
02-18-2000	Sebaceous hyperplasia	Skin; neck, right upper	Excision
03-21-2000	Squamous cell carcinoma	Skin; ala of nose	Excision
12-08-2000	Sebaceous adenoma	Skin; edge of left lower eyelid	Excision
12-19-2000	Sebaceous gland hyperplasia	Skin; left lower eyelid, conjunctival side, medial	Excision
	Sebaceous adenoma	Skin; left lower eyelid, conjunctival side, lateral	Excision
01-23-2001	Sebaceous hyperplasia	Skin; left upper eyelid	Excision
05-01-2001	Squamous cell carcinoma	Skin; right clavicle	Excision
05-25-2001	Sebaceous lobular hyperplasia & small sebaceous adenomas	Skin; nose, upper	Excision
	Sebaceous gland hyperplasia	Skin; nose, down	Excision
		Skin; back	Excision
06-01-2001	Sebaceous hyperplasia	Skin; right cheek	Excision
		Skin; left cheek	Excision
06-13-2001	Sebaceous hyperplasia	Skin; right forearm	Excision
09-14-2001	Sebaceous hyperplasia	Skin; left cheek	Excision
		Skin; right cheek	Excision
09-19-2001	Sebaceous hyperplasia	Skin; left side of abdomen	Excision
09-24-2001	Sebaceous gland hyperplasia	Skin; medial right superior scapula	Excision
10-05-2001	Hyperplastic polyps	Rectosigmoid and descending colon	Polypectomies
03-01-2002	Squamous cell carcinoma, well-differentiated	Skin; back	Excision
03-08-2002	Sebaceous adenoma	Skin; outer right thigh	Excision
		Skin; mid right forearm	Excision
		Skin; mid right back	Excision
07-23-2002	Squamous cell carcinoma, well-differentiated	Skin; left thigh	Excision
08-14-2002	Tubular adenoma with focal moderate dysplasia	Ascending/transverse colon	Polypectomies
11-29-2002	Sebaceous cell hyperplasia	Skin; chest	Excision
	Sebaceous adenoma	Skin; right lower arm	Excision
	Sebaceous gland hyperplasia	Skin; lower arm	Excision
12-13-2002	Sebaceous gland hyperplasia	Skin; right temple	Excision
		Skin; left upper nose	Excision
		Skin; left lower nose	Excision
		Skin; left forearm	Excision
08-27-2003	Sebaceous adenoma	Skin and subcutaneous tissue; axilla	Excision
	Atypical sebaceous adenoma	Skin and subcutaneous tissue; right scapula	Excision
09-25-2003	Hyperplastic polyps	Rectum and sigmoid	Polypectomy
04-27-2004	Atypical proliferating trichilemmal cyst	Skin and subcutaneous tissue; face	Excision
01-17-2005	Hyperplastic polyp	Sigmoid colon	Polypectomy
09-14-2005	Sebaceous adenoma	Skin; right scapula	Excision
		Skin; left scapula	Excision
		Skin; right mid-back line	Excision
		Skin; right lumbar	Excision
	Sebaceous epithelioma (basal cell carcinoma with sebaceous cell differentiation)	Skin; right gluteus	Excision
	Squamous cell carcinoma, well-differentiated	Skin; left nasal side	Excision
		Skin; left upper lip	Excision
10-31-2005	Tubular adenoma with extensive high-grade dysplasia; one fragment showing intramucosal adenocarcinoma, well-differentiated	Transverse colon	Partial polypectomy
12-09-2005	Multiple hyperplastic polyps	Rectum	Polypectomy
12-14-2005	Sebaceous adenoma	Skin and subcutaneous tissue; lower back	Excision
12-21-2005	Sebaceous gland hyperplasia	Skin and subcutaneous tissue; neck	Excision
01-12-2006	Tubulo-villous adenoma	Transverse colon	Resection
01-18-2006	Sebaceous gland hyperplasia	Skin; forehead, left front side	Excision
	Sebaceous adenoma	Skin and subcutaneous tissue; sternum	Excision

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Table 1. List of new hyperplastic or neoplastic lesions detected during the period of detailed observation. (Cont'd)

Date (MM-DD-YYYY)	Diagnosis	Site	Treatment
02-20-2006	Tubulovillous adenoma, including a small focus of well-differentiated adenocarcinoma.	Transverse colon	Total abdominal colectomy with ileorectal anastomosis
05-10-2006	Sebaceous gland hyperplasia	Skin; lower back	Excision
		Skin; mid-back	Excision
		Skin; left shoulder	Excision
		Skin; neck	Excision
05-30-2006	Sebaceous carcinoma	Skin and subcutaneous tissue; left back	Excision
	Sebaceous gland hyperplasia	Skin and subcutaneous tissue; left back	Excision
07-05-2006	Sebaceous gland hyperplasia/sebaceous adenoma	Skin and subcutaneous tissue; right anterior chest	Excision
08-02-2006	Sebaceous adenoma with mild degree of cellular atypism	Skin; left hand	Excision
	Sebaceous carcinoma	Skin; left flank	Excision
	Atypical sebaceous adenoma	Skin; left flank	Excision
11-28-2006	Sebaceous and germinative cell hyperplasia	Skin; right lower eyelid	Excision
12-05-2006	Sebaceous gland hyperplasia	Skin; left upper eyelid, conjunctival side	Excision
01-15-2007	Sebaceous adenoma	Skin; right forearm	Excision
03-28-2007	Sebaceous hyperplasia	Skin; spine	Excision
		Skin; lower back	Excision
		Skin; right chest	Excision
	Sebaceous adenoma	Skin; right chest	Excision
		Skin; left chest	Excision
		Skin; abdomen	Excision
05-08-2007	Sebaceous adenoma	Skin; right lower eyelid	Excision
12-18-2007	Sebaceous gland hyperplasia	Skin; tip of nose	Excision
		Skin; right eyebrow	Excision
		Skin; left forehead	Excision
03-26-2008	Sebaceous adenoma	Skin; abdomen	Excision
04-22-2008	Small sebaceous adenoma	Skin and subcutaneous tissue; right upper neck	Excision
	Sebaceous gland hyperplasia, multifocal	Skin and subcutaneous tissue; right upper neck	Excision
		Skin and subcutaneous tissue; right lower neck	Excision
06-03-2008	Squamous cell carcinoma	Skin; right medial canthus	Excision
06-03-2008	Squamous cell carcinoma, well-differentiated	Skin; right nasal bridge	Excision
10-28-2008	Sebaceous adenoma	Skin; right lower eyelid	Excision
02-11-2009	Sebaceous epithelioma	Skin; left axilla	Excision
		Skin; right buttock	Excision
		Skin; left buttock	Excision
03-10-2009	Sebaceous hyperplasia	Skin; right lower eyelid	Excision
03-19-2009	Sebaceous and germinative cellular hyperplasia	Skin; left neck	Excision
08-26-2009	Sebaceous gland hyperplasia	Skin; scrotum	Excision
		Skin; left arm	Excision
10-28-2009	Focal high-grade dysplasia and extensive low-grade dysplasia	Duodenum	Resection
11-19-2009	Carcinoma	Duodenum	Resection
	Invasive adenocarcinoma, moderately differentiated	Jejunum	Resection
	Invasive adenocarcinoma, moderately to poorly differentiated	Small bowel	Resection
05-12-2010	Sebaceous adenoma	Skin; right upper back	Excision
	Keratoacanthoma	Skin; left arm	Excision
11-23-2010	Sebaceous adenoma	Skin; right tip of nose	Excision
12-07-2010	Squamous cell carcinoma, well-differentiated	Skin; right forearm	Excision
02-16-2011	Squamous cell carcinoma, well-differentiated	Skin; right forearm	Excision
11-17-2011	Squamous cell carcinoma, well-differentiated	Skin; right inner thigh	Excision
12-07-2011	Squamous cell carcinoma, well-differentiated	Skin; medial left buttock	Excision
		Skin; right scapula	Excision
	Squamous cell carcinoma, moderately differentiated	Skin; lateral left buttock	Excision
01-25-2012	Squamous cell carcinoma, well-differentiated	Skin; left cheek	Excision
07-18-2012	Squamous cell carcinoma, well-differentiated	Skin; left upper chest	Excision
07-18-2012	Keratinizing squamous cell carcinoma, well-differentiated	Skin; left upper chest	Excision

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Table 1. List of new hyperplastic or neoplastic lesions detected during the period of detailed observation. (Cont'd)

Date (MM-DD-YYYY)	Diagnosis	Site	Treatment
04-11-2013	Squamous cell carcinoma	Skin; left superior buttock	Excision
	Sebaceous epithelioma	Skin; left inferior buttock	Excision
04-25-2013	Squamous cell carcinoma, well-differentiated	Skin; left upper nasal sidewall	Excision
	Squamous cell carcinoma	Skin; left nasal sidewall/dorsum	Excision
05-02-2013	Sebaceous carcinoma infiltrating in dermis	Skin; left inguinal area	Excision
	Sebaceous adenoma	Skin; left inguinal area	Excision
05-27-2013	Sebaceous carcinoma	Skin; left mid-back	Excision
06-19-2013	Sebaceous adenoma	Skin; mid-back, slightly left	Excision
08-19-2013	Overlying squamous cell carcinoma, keratinizing and moderately differentiated	Skin; left knee	Excision
08-27-2013	Adenoma	Small bowel	Small bowel resection
10-25-2013	Tubular adenoma	Duodenum	Polypectomy
04-29-2015	Sebaceous carcinoma	Skin; left elbow	Excision
11-16-2015	Squamous cell carcinoma, well differentiated	Skin; right shoulder	Excision
11-26-2015	Squamous cell carcinoma	Skin; right shoulder	Excision
02-09-2017	Squamous cell carcinoma, well differentiated	Skin, right popliteal fossa	Excision
02-16-2017	Squamous cell carcinoma, well differentiated	Skin; right superior calf	Excision
03-16-2017	Adenocarcinoma	Jejunum	Small bowel resection and reanastomosis
04-12-2017	Squamous cell carcinoma, well differentiated	Skin; left leg	Excision
07-24-2017	Squamous cell carcinoma, moderately differentiated, invasive	Skin; right upper lateral arm	Excision
08-30-2017	Metastatic poorly differentiated sebaceous carcinoma	Pelvic node	Excision
11-28-2017	Noninvasive, low-grade papillary urothelial carcinoma	Distal right ureter	Biopsy, gemcitabine + radiotherapy
	Invasive papillary urothelial carcinoma	Right ureterovesical junction	
10-11-2017	Sebaceous epithelioma	Skin; left superior buttock	Excision
11-21-2017	Metastatic sebaceous carcinoma	Soft tissue; pelvis	Excision
12-07-2017	Squamous cell carcinoma, well-differentiated	Skin; left chest	Excision
01-05-2018	Prostate adenocarcinoma, Gleason grade 9	Prostate, right lateral base, and left lateral apex	Radiotherapy + androgen deprivation therapy

truncating germline mutation was identified in Segment 1 of the *MSH2* gene. DNA sequencing revealed the presence of a splice site mutation (1661+1G>T). This result was consistent with the clinical presentation that showed features of the Muir–Torre syndrome.

The patient was subsequently followed carefully by dermatology, urology, and gastroenterology consultants. **Table 1** provides a list of lesions detected during the period of detailed observation, starting in February 1999 and extending to March 2020. A total of 136 neoplasms, predominately premalignant (or hyperplastic), were detected over the 18-year period (mean 7.4 neoplasms/year, range 2–26, median 12), as shown in **Fig. 1**. Major surgical procedures included a right colectomy in 1991 for colon polyps and Dukes Stage C colon cancer (carried out at a community hospital before referral to our center), and small bowel resections in 2006, 2009, 2013, as well as 2017 for neoplastic lesions as noted in **Table 1**. He also had numerous smaller procedures, mainly excision of skin neoplasms and multiple polypectomies.

In November 2017, the patient was found to have invasive papillary urothelial carcinoma involving the right ureterovesical junction as well as Gleason grade 9 prostate cancer. Neoplasia of the genito urinary system has been previously described in Lynch syndrome, but we did not have access to tissue to allow us to determine whether a DNA repair deficit was involved in the pathogenesis of these cancers in our patient. Surgery was considered but was refused by the patient. Therefore, he received a multimodal treatment regimen comprised of chemo–radiotherapy, followed by 1 year of immunotherapy administration with pembrolizumab, 200 mg i.v. every 3 weeks. This was felt to be an optimal treatment program, given that Muir–Torre syndrome is associated with a high-tumor mutational burden, which in turn is associated with high probability of utility of immune checkpoint blockade treatment. Specifically, he received 75 mg/m^2 of intravenous gemcitabine weekly during radiotherapy, and 60 Gy delivered in 20 fractions to the prostate, 50 Gy delivered in 20 fractions to the bladder, and 40 Gy delivered in 20 fractions to the pelvic nodes. He also received androgen deprivation therapy for the prostate cancer. The patient experienced significant gastrointestinal toxicity related to the chemo–radiation treatments, which was managed symptomatically and resolved prior to the commencement of pembrolizumab treatments in April 2018. The pembrolizumab treatment (200 mg i.v. every 3 weeks) was well-tolerated and continued for 1 year.

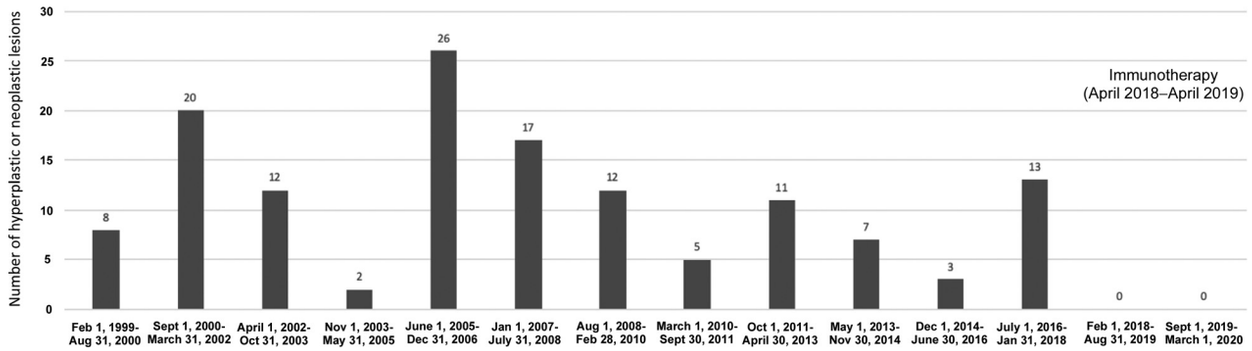

Figure 1.
Twenty one–year timeline showing number of hyperplastic or neoplastic lesions from February 1999–March, 2020.

During and following the 12 months of immunotherapy, with continuous multidisciplinary surveillance similar or even more intensive to that undertaken since 1999, we noticed an absence of new neoplasms, including both premalignant lesions and cancers. Cystoscopy and imaging carried out in February 2020 confirmed absence of residual urothelial cancer. In view of the risk of autoimmune disease that might be associated with continuous immunotherapy administration for an indefinite period and due to the absence of detectable neoplasia in the patient, it was decided to stop immunotherapy in April 2019.

As of the time of preparation of this article, the unusual period of absence of new epithelial malignancies continued from initiation of pembrolizumab in April 2018 until March 2020, for a total of 22 months without a new diagnosis of cancer or of a premalignant hyperplastic lesion. With respect to his Gleason grade 9 prostate cancer, he remains without detectable disease with a PSA of zero, but this may be attributable in whole or in part to an excellent response to androgen deprivation therapy given simultaneously with immunotherapy. An FDG-PET scan carried out on November 14, 2019 was also normal. This contrasts with the patient's prior history characterized by a mean of 7.5 new neoplasms per year.

Discussion

This case is consistent with the possibility that immune checkpoint therapy reduces the risk of developing clinically detectable cancers in patients with Lynch syndrome, and possibly in those with other DNA repair deficits. A more convincing demonstration would obviously require longer follow-up, additional molecular, pathologic, and immunologic characterization of lesions observed, and more patients, but such a study would be challenging to execute.

We speculate that checkpoint blockade does not actually block carcinogenesis at the cellular level; it is more likely that it increases the probability that a host immune response will eliminate hyperplastic or neoplastic clones before they become clinically detectable. While pembrolizumab was prescribed for bladder cancer treatment, our patient's history raises the possibility that treatment may have also acted as an immunologic "cancer interception" strategy (15) effectively reducing risk of developing new cancers and new clinically detectable hyperplastic lesions.

A practical issue in the management of this patient and in any other situation where immune checkpoint blockade would be used for cancer prevention concerns the duration of therapy. Indefinite treatment would increase the risk of autoimmune toxicity (16). It may be sufficient to provide pulsed immunotherapy on a periodic basis to extinguish accumulating neoplasms before they become clinically detectable.

It is likely that any utility of immune checkpoint blockade for cancer prevention would be most obvious in patients at high risk because of inherited DNA repair deficits known to lead to increased mutational burden in each cell at risk for transformation. However, because some cancers have high-mutational burden in the absence of inherited deficits in DNA repair, and furthermore, because increased tumor mutational burden is not always required for advanced cancers to respond to checkpoint inhibition, we cannot rule out the possibility that checkpoint inhibition could reduce cancer risk in other populations. Although we recognize the inherent limitations of an "$n = 1$" case report, this patient's history suggests that "immuno-interception" as a strategy to reduce cancer risk deserves further study.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

One of the Editors-in-Chief of *Cancer Prevention Research* is an author on this article. In keeping with AACR editorial policy, a senior member of the *Cancer Prevention Research* editorial team managed the consideration process for this submission and independently rendered the final decision concerning acceptability.

Authors' Contributions

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