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Cutaneous manifestations of genitourinary malignancy

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ABSTRACT

Genitourinary cancers are associated with a range of cutaneous syndromes, which can reflect direct metastatic spread, non-metastatic manifestations of malignancy or the consequences of treatment. More than 220,000 new cases of prostate cancer occur each year in the United States, and thus the associations with cutaneous involvement are quite well documented—rare metastatic spread, vasculitic and hemorrhagic syndromes. Cancers of the bladder and kidney may be associated with direct cutaneous metastases, vasculitic syndromes, hereditary leiomyomatosis, and other familial syndromes. Testicular cancer occasionally metastasizes to the skin but more commonly is associated with the dysplastic nevus (multiple atypical nevus) syndrome. A structured approach to history-taking, examination, and investigation is essential for optimal management, especially when these syndromes precede the diagnosis of a known malignancy. A brief review of the more common iatrogenic cutaneous complications is provided, and includes Raynaud's phenomenon, purpura, rash, hand-foot syndrome, the consequences of marrow failure, and bleomycin-induced pigmentation.

1. Introduction

The group of tumors classified as "genitourinary cancers", including cancers of the prostate, bladder, kidney, testis, urethra, ureters and penis account for nearly 400,000 new cases per year in the United States [1]. Cancers of the prostate, bladder, kidney, and testis are the most common of the genitourinary cancers, and thus relatively robust data exist that link them to cutaneous manifestations of malignancy [2–8], although much of the literature is dominated by anecdotal lists and case reports. For the less common genitourinary cancers, such as cancers of urethra and penis, the available information is purely anecdotal, and is not covered in detail here.

Large clinical and autopsy series have attempted to quantify the more common cutaneous associations of genitourinary cancer. Krathen et al [2] conducted a meta-analysis of cutaneous metastases from tumor registries and autopsy studies, concluding that the overall incidence of cutaneous metastases is about 5.3%, with breast cancer being the most common. Cancers of the kidney, bladder, and prostate, when considering patients with cutaneous metastases per autopsy cases, were among the most common, respectively, with rates of 4.0%, 3.6%, and 0.7% [2]. Thiers et al [3], in a broad review of cutaneous manifestations of internal malignancy, noted the importance of inherited syndromes, hormone-secreting tumors, and the proliferative and inflammatory dermatoses, many of which are manifest in protean ways. Several large series have produced similar incidence figures [4–6]. When attempting to calculate the frequency of these phenomena, it is important to recognize that the literature is heavily influenced by the nature of the referral practice and the clinical interests of the authors contributing their experience, and there is considerable data recycling in the various reviews.

1.1. Systematic approach to diagnosis

Given the paucity of large data sets that yield definitive correlations between cutaneous syndromes and genitourinary malignancy, it is particularly important to employ a structured or systematic approach to diagnosis and management of the clinical scenarios that arise. In broad terms, I prefer to structure the cutaneous manifestations of genitourinary malignancy thus:

a) Metastases to the skin and adjacent tissues;
b) non-metastatic manifestations, such as genetic, metabolic, immunological, vasculitic or endocrine syndromes;
c) iatrogenic manifestations associated with cancer or other therapy.

It is essential for the clinician to obtain a thorough history as appropriate for any oncologic condition but also focusing on intercurrent, past or present medical system disorders that might

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Table 1
Checklist for cutaneous manifestations of genitourinary malignancy.

Cutaneous metastases	
*	Discrete pigmented lesions
*	Infiltrative lesions
*	Subcutaneous mass lesions
*	Ulcers
Non-metastatic manifestations	
*	Vasculitic lesions—palpable purpura, nonpalpable ecchymoses
*	Fibromata and other cutaneous mass lesions
*	Calcinosis and calcification
*	Pigmentation
*	Syndromes, eg, Cushing's, Birt-Hogg-Dube, etc
*	Known clinical associations eg, male pattern baldness and prostate cancer; multiple atypical nevi and germ cell tumors
Iatrogenic manifestations	
*	Raynaud's phenomenon
*	Pigmentation, eg, post-bleomycin, cutaneous rash/pigmentation after intravesical mitomycin C
*	Endocrine features, eg, organ dysfunction corticosteroid effects
*	Pallor, bruising, eg, associated with pancytopenia after chemotherapy
*	Rash—methotrexate toxicity
*	Muco-cutaneous ulcers, eg, associated with methotrexate toxicity, infection, pancytopenia

explain the skin manifestations, family history, medication history, history of prior transient or continuing cutaneous diatheses (and their potential precipitants), and past allergic reactions. It is also important to elucidate the timing, potential precipitant(s) and extent of the present cutaneous features, and whether this has been a relapsing/remitting condition.

The medical examination is equally crucial, and should include the standard aspects of a general clinical examination, also including specific items associated with the malignancy under consideration, but also augmented by specific contextual additions. For example, as detailed in the specific sections below, it is important to assess specifically the presence of multiple atypical nevi, palpable purpura [7-10], signs of endocrine syndromes (eg, Cushing's syndrome), hemorrhagic diatheses [7-13], pigmentation, pallor, and a host of cutaneous lumps and bumps, within the skin and subcutaneous regions. Adequate time must be allocated for a detailed physical examination, and it is often useful to employ a pre-determined template to avoid important omissions (Table 1).

When a cutaneous lesion is identified, it usually is prudent to arrange for a biopsy to define clearly its exact nature. Of course, the patient should only be subjected to this invasive procedure if there is a good rationale for it, namely, if defining the nature of the lesion will alter management. For example, if a patient with widespread, proven metastatic genitourinary cancer is noted to have a cutaneous lesion or lesions, and systemic treatment is planned, it is probably not necessary to add an additional biopsy to confirm the presence of skin metastases. By contrast, if the same patient develops multiple purpuric or coalescing, infiltrative lesions after treatment has been initiated, it may be important to determine whether this represents part of the underlying malignancy, an iatrogenic complication, or tumor progression, and thus biopsy may well be justified. The cutaneous associations with underlying solid tumors can be subtle and the lesions can constitute challenging histopathological diagnostic problems, and thus it is important to secure an opinion from an experienced dermatopathologist who is experienced in this domain. It is often wise to discuss the case with the pathologist prior to biopsy to ensure that the optimal preparation and fixation is implemented to facilitate the necessary diagnostic tests.

2. Prostate cancer

2.1. Adenocarcinoma

Prostate cancer is, by far, the most common genitourinary malignancy, with about 220,000 new cases reported each year in the United States [1]. The most frequent histological type is classical adenocarcinoma, representing more than 80%–85% of new cases, and associated with the production of the tumor marker, prostate specific antigen. The most frequent presentation is so-called "early stage" or localized disease, with tumor restricted to the prostate, with less frequent occurrence of locally advanced (stages T2–4) disease extending to surrounding structures.

In general, the symptoms associated with clinically non-metastatic prostate cancer relate to the extent of local tumor. Rarely, a patient with localized disease will experience systemic symptoms that constitute non-metastatic manifestations of the disease. I have seen patients who have presented with pruritus as the sole symptom, and physical examination has revealed a localized prostate cancer; after radical prostatectomy, the pruritus has completely resolved! However, it is important to note that systemic features of this type are more often associated with metastatic prostate cancer.

2.1.1. *Cutaneous metastases*

About 20% of incident cases are regional or metastatic at first presentation [1]. The classical sites of metastasis include bones and lymph nodes, with occasional involvement of other sites, such as lung, liver, and brain. Soft tissue metastases are often associated with an uncommon histological type, neuroendocrine or small cell anaplastic prostate cancer (see below), although they may also be present in classical adenocarcinoma in association with widespread metastatic disease. In a series of more than 10,000 cases of genitourinary cancer, cutaneous metastases were recorded in 1.3%, and from prostate cancer in only 0.36% [4]; others have reported the incidence to be 0.7% [2].

Cutaneous metastases from prostate cancer are most commonly discrete, single or multiple nodular lesions, although they may less commonly be diffuse and infiltrative.

2.1.2. *Syndromes*

Advanced prostate cancer is one of the great mimics of internal medicine; like tuberculosis, syphilis, the connective tissue disorders, and HIV, this malignancy can sometimes manifest itself with a range of non-specific symptoms (pruritus, sweats, fever, anorexia, weight loss and cachexia, fatigue), protean rashes, and paradoxical laboratory abnormalities. It has been occasionally shown to manifest itself with migratory superficial thrombophlebitis or deep venous and rarely arterial thrombosis [2,3,12,13]. Similarly a range of inflammatory changes and necrosis of small