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Inflammatory dermatoses, infections and drug eruptions are the most common skin conditions in hospitalized cancer patients

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Abstract

Background—Dermatologic conditions cause morbidity and mortality among hospitalized cancer patients. An improved understanding is critical for implementing clinical and research programs in inpatient oncodermatology.

Objective—To characterize inpatient dermatology consultations at a large comprehensive cancer center.

Methods—Retrospective database query of new admissions and medical record review of initial inpatient dermatology consultations comparing consulted inpatients with non-consulted inpatients from January-December 2015.

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Results—In total, 412 of 11,533 inpatients received 471 dermatology consultations (54% male, median age 59.5). Patients with hematologic cancers were six times more likely to receive dermatologic consultations compared to non-hematologic cancers (OR 6.56, 95% CI (5.35, 8.05), $p < .0001$). Patients consulted by dermatology had significantly longer length of stay (median 11 vs 5 days, $p < .0001$). Among the 645 dermatologic conditions diagnosed, the most common categories were inflammatory diseases, infections, and drug reactions; the most frequent conditions were contact dermatitis, herpes zoster, and chemotherapy-induced drug eruptions.

Limitations—The study's retrospective nature and single-institutional setting are potential limitations.

Conclusion—Hematologic malignancies are a significant risk factor for dermatology inpatient consultations. A significantly longer length of stay was associated with dermatology consultations, suggesting high comorbidities in these patients. Increased dermatologic care of these inpatients may improve quality of life, dermatologic health, and ability to receive anticancer agents.

Keywords

inpatient; consultation; referral; cancer; oncodermatology; hematologic; adverse event; infection; inflammatory

Introduction

Patients with cancer often suffer cutaneous manifestations of internal disease and dermatologic adverse events (dAEs) from anticancer therapies including systemic agents, radiation, surgery, and stem cell transplants, which diminish health-related quality of life in the outpatient setting and impact cancer treatment adherence.¹ For instance, epidermal growth factor receptor (EGFR) inhibitors alone have been associated with a papulopustular rash in 45–100% of patients, xerosis and pruritus in 12–16% of patients, and nail changes in up to 17% of patients.^{2,3} In response, the field of supportive oncodermatology has grown to address the dynamic problems posed by patients that encounter multiple and often investigational treatment modalities.^{4,5} However, the most effective role for supportive oncodermatology in inpatient care has not been defined and is under investigation prospectively.

Inpatient consultative dermatologic services play an important and challenging role in the diagnosis and management of dAEs that emerge in patients hospitalized for cancer treatment, complications of therapy, or palliative supportive care.⁶ Despite declining dermatologist involvement in hospital consultations,⁷ inpatient dermatology consultations have been shown to have a significant effect on diagnostic accuracy and the management of skin conditions in the hospital setting.^{8–10} By facilitating prompt and accurate recognition and interpretation of skin conditions as well as effective dermatologic treatment in hospitalized patients, inpatient consultative dermatology services perform a vital function unmet by non-specialty services, ultimately having a meaningful impact on hospital outcomes including length of stay and 1-year readmission rates.^{8,11,12}

Whereas the epidemiology of skin disease has been studied in hospitalized medical,^{8,10–18} pediatric,^{19–22} and hematologic oncology patients,^{23–25} there is limited data²⁶ describing

dAEs and other skin conditions in hospitalized patients undergoing treatment for cancer as well as the role of dermatology consultations in their management. Given the potential impact of inpatient dermatology consultations on maintaining quality of life, dermatologic health, and ability to receive antineoplastic therapies, an increased understanding of demographic and disease-specific factors would be critical towards the optimization of supportive inpatient oncodermatology clinical and research efforts.^{1,4,11} We sought to characterize and evaluate the need for inpatient dermatology consultations at a major comprehensive cancer center by studying the spectrum of diseases encountered, the circumstances in which cancer patients were found to have cutaneous concerns necessitating consultation, and the recommendations provided by consulting dermatologists in ensuring quality of care.

Methods

Study Sample

Following approval by the Institutional Review Board of Memorial Sloan Kettering Cancer Center (protocol 16-410), an observational retrospective chart review was conducted by extracting all inpatient dermatology consultations at Memorial Sloan Kettering Cancer Center (MSK) in the twelve-month period from January 1, 2015 to December 31, 2015 using a query of MSK's Health Information System and consultation log maintained by the Dermatology service staff. A total of 11,533 unique inpatients with a history of malignancy were admitted for at least 24 hours at MSK and 412 of them received inpatient dermatology consultations. Forty-two of these patients received more than one inpatient dermatology consultation in 2015.

A total of 824 dermatology consultation records were identified; 320 follow up consultations were excluded leaving 504 initial consultations for further screening. After chart review to exclude non-admitted urgent care center consultations and patients without a history of malignancy, 471 consultation records documenting the 412 unique patients remained for final analysis. Relevant data were abstracted from each patient's electronic medical record including demographics, primary cancer diagnosis and cancer treatment, service requesting consultation, reason for consultation, dermatologic diagnosis, and consulting dermatologist recommendations. If a patient had more than one cancer diagnosis, the active or most recent cancer diagnosis was used. Final dermatologic diagnosis was abstracted from the dermatologist's initial consultation note and was correlated with skin biopsy and culture results in those consultations that recommended biopsy or culture. The reporting cutoff for cancer treatment was made at 30 days pre-consultation because dAEs and hypersensitivity reactions are likely to surface within 30 days of administration.^{27,28} For the purposes of this study, prescriptions recommended by the dermatologist included pharmaceutical interventions while emollients, lymphedema therapy, and wound care were categorized as non-prescription recommendations. Anticancer pharmaceutical treatment was categorized into cytotoxic, targeted, immunotherapy, hormonal, investigational, and combination respectively: traditional, nonselective cytotoxic chemotherapy (e.g. cytarabine, paclitaxel); novel, targeted small-molecule inhibitors of specific oncologic targets (e.g. erlotinib, sorafenib); immunotherapy in the form of monoclonal antibodies against cancer-associated

molecules (e.g. rituximab, nivolumab); hormonal therapy exerting effects on endocrine hormone-receptor positive tumors (e.g. tamoxifen, anastrozole); investigational agents not yet classifiable; and combination therapy involving agents from two or more categories. The inpatient (Tables I and II) and the consultation (Tables III and IV) characteristics were described.

Statistical Analysis

Patient characteristics were compared between groups using the Chi-square test for categorical variables and the Wilcoxon rank sum test for continuous variables. Those characteristics found to be significantly associated with the likelihood of receiving a dermatology consultation (age, gender, and primary cancer diagnosis) were further analyzed in a multivariable logistic regression model to assess for independent association. All statistical analyses performed in SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

In 2015, MSK admitted 11,533 unique patients for a median stay of 5 days (interquartile range (IQR) 3–8, range 2–152). A total of 412 inpatients with a history of malignancy required a dermatology consultation; the median age (IQR) was 59.5 (46–69) with 47% having a hematologic malignancy. In terms of demographics, patients necessitating dermatology consultations were similar to those admitted for treatment at MSK overall. However, primary cancer diagnosis was significantly associated with dermatologic consultation ($p<.0001$). Compared to all other admitted patients, patients necessitating consultation more likely had a primary diagnosis of leukemia (27% vs. 4%) and lymphoma (17% vs 6%). Patients with a gastrointestinal primary cancer diagnosis were least likely to receive a dermatology consultation (9% vs 27%). This association remained significant in multivariable analysis controlling for age and gender ($p<.0001$). Patients with hematologic malignancies were six times more likely to have received a dermatologic consultation compared to patients with non-hematologic malignancies (OR 6.56, 95%CI (5.35, 8.05)). In addition, patients requiring dermatology consultation had a higher death rate during admission (9% vs 2%, $p<.0001$) and a longer median length of stay (LOS) of 11 days vs 5 days for other MSK inpatients ($p<.0001$; Table I). Examining the most recent admission, the median interval from admission until dermatology consultation was 3 days (IQR 1–10) (N=412). Among patients whose reason for most recent admission included any dermatologic issues (N=77), the median interval from admission to dermatology consultation was 1 day (IQR 1–3).

During this period, 42 (10%) patients who received dermatology consultation were seen at multiple distinct consultations during distinct admission periods. Compared with patients receiving one dermatology consultation in 2015, patients with multiple dermatology consultations were more likely to have a diagnosis of leukemia (50% vs 24%) and lymphoma (29% vs 15%) ($p=.001$; Table II).

There were 471 initial consultations of the 412 patients with primary cancer diagnoses (Table III). In 294 (62%) consultations, systemic anticancer treatment was received in the 30 days prior to consultation. The most common therapy types were cytotoxic (n=135, 46%),

targeted (n=52, 18%), and combination (n=79, 27%) chemotherapy. Some members of the cohort had undergone radiation therapy (n=41, 9%) and surgery (n=74, 16%) within 30 days of consultation. Of note, 25% (n=118) of consultations were completed on patients whose reason for admission included a cutaneous concern. The services that most frequently requested inpatient dermatology consultation were Hematology/Oncology (44%), Solid Tumor Oncology (27%), and Surgery (15%).

Table IV details the final dermatologic diagnoses made by the consulting dermatologists. There were 645 diagnoses for the 471 consultations, which reflect that in many cases multiple skin conditions were identified during a single consultation. Inflammatory (27%), infection (24%), and drug reactions (17%) comprised the most common diagnostic groups. Across all diagnoses, the specific conditions of herpes zoster (4%) and contact dermatitis (3%) occurred most frequently. The most common diagnostic groups in the 335 dermatologic diagnoses in patients with hematologic malignancies were inflammatory (28%), infection (23%), drug reaction (13%), and neoplasm (13%). The most frequent offending agents implicated in the 111 drug reactions were of chemotherapeutic (36%) and antimicrobial (26%) classes. Of the forty drug reactions attributed to chemotherapy, 58% (n=23) were related to cytotoxic agents, 18% (n=7) to immunotherapy, 13% (n=5) to targeted agents, 7% (n=3) were unspecified, and 5% (n=2) were investigational agents.

Biopsy and culture were recommended by the dermatologist for diagnosis in 18% (n=84) and 25% (n=120) of dermatology consultations, respectively. The majority of patients required topical therapy alone (n=199, 42%) and the mean number of prescriptions recommended by the dermatologist was 1.6 (SD=1.3). Dermatology consultation prompted additional diagnostic evaluations (n=32, 7%), procedural interventions (n=19, 4%, most commonly ultrasonography (8) and incision and drainage (4)), consultation of another service (n=19, 4%, i.e. allergy and immunology (6) and ophthalmology (3)), as well as follow-up with outpatient dermatology (n=46, 10%).

Discussion

Inflammatory (27%) and infectious (24%) skin conditions were the most common conditions found at inpatient dermatologic evaluation; additionally, 17% of the skin conditions observed in this cohort were dAE attributable to pharmacologic therapy. These findings are comparable with previous studies examining the epidemiology of inpatient dermatology consultations in non-cancer specific hospitals as well as hematologic oncology inpatients.^{9,18,23–25,29} Nonetheless, the patients hospitalized in a non-cancer specific hospital were found to have a greater relative incidence of inflammatory conditions (31% vs 27%) and less frequent drug reactions (12% vs 17%) compared to the MSK cohort.¹⁸

Inpatients with hematologic malignancies may develop various skin conditions including neutrophilic dermatoses, graft-versus-host disease, and morbilliform drug eruptions.²⁵ In our study, 47% of inpatients requiring dermatology consultation had an underlying hematologic malignancy. Similar results were previously reported, where 52% of inpatients at a cancer center receiving dermatology consultation had a primary diagnosis of leukemia or lymphoma.²⁶ While one study of hematologic oncology inpatients showed a higher number

of drug reactions (38% vs 13%) and a less frequent rate of infections (15% vs 23%)²³, another study demonstrated a more similar rate of cutaneous drug reactions and infections (22%) in patients with hematologic malignancies when compared to our study population.²⁵

Hematologic cancer patients, who often undergo intense treatment regimens including induction chemotherapy, stem cell transplants, and prophylactic antibiotics, are prone to skin infections and dAEs due to their immunocompromised state and exposure to high numbers of systemic therapies.³⁰ These results suggest that this group of patients may need dermatologic intervention to promptly diagnose skin conditions that may arise during their hospital stay.

Furthermore, this study may help identify underlying malignancies that predispose patients to specific dermatologic conditions requiring the expertise of dermatologists for diagnosis and management. The need for dermatology consultation was significantly associated with primary cancer diagnosis independent of patient age or gender, suggesting that patients with leukemia and lymphoma require dermatologist input in their management more frequently and may be at a greater risk for dAEs. Patients with hematologic malignancies may benefit from a decreased threshold for dermatology consultation and close monitoring by the dermatologists, potentially expediting diagnosis and improving management and outcomes. On the other hand, the relative infrequency of dermatology consultations for patients with gastrointestinal, genitourinary, and lung cancers may reflect a decreased need for dermatology involvement or decreased risk for skin disease necessitating inpatient dermatology consultation in these patients.

Hospital length of stay was significantly associated with the need for dermatology consultation ($p < .0001$). Of all hospitalized patients at MSK in 2015, the median LOS was 6 days longer in patients who required dermatology consultation. The increased LOS in patients who required dermatology consultation may reflect their increased comorbidity burden, greater severity of dermatologic disease, or higher propensity to develop skin conditions with more medication and nosocomial exposures during the longer hospitalization duration. Additionally, the presence of any admission-consultation interval delay may tend to elongate the estimated LOS in the cohort of patients receiving consultations. It is further possible that delayed dermatologic consultation could delay discharge since the median admission-consultation interval was 3 days. Recently, dermatology consultations were associated with a reduction in hospital LOS by 2.64 days among patients admitted for inflammatory skin disorders when adjusted for admission-to-consultation lag time.¹¹ However, our assessment of the need for dermatology consultation is not directly comparable because we focused on cancer patients admitted for both cutaneous and non-cutaneous concerns and we did not evaluate how dermatologic consultation itself impacted LOS.

The majority of patients (66%) were prescribed topical therapy for their skin conditions and 38% required systemic therapy, which may reflect that most skin conditions encountered did not have significant systemic involvement and were managed without aggressive therapies. As suggested elsewhere,¹⁰ the extent of topical therapy may also indicate that the majority of consultations did not require extensive follow up because most consultations were for

uncomplicated skin conditions. However, the prescription rates in our study were greater than a previous study of hospitalized patients receiving dermatology consultation (52% topical therapy, 26% systemic therapy).³¹ Regardless, dermatologists managed skin conditions without the need for further laboratory testing in most patients: the most frequent test recommended was superficial microbial culture in only 25% of consultations, which parallels the rate of infections in the cohort. The present study's findings that 42% of consultations recommended some form of additional diagnostic testing falls within the range reported in the reviewed literature of 6%¹⁷ to 60%.²⁵

Limitations of the study include its retrospective nature, reliance on electronic medical records, and single-hospital scope. We are not able to comment on the prevalence of skin disease in all hospitalized cancer patients at MSK due to our focus on only those cases in which a consultation was deemed necessary by the primary team. Additionally, placement of specific dermatologic diseases into groups before analysis inevitably introduces bias. Further analysis is required to assess the relationship between specific cancer comorbidities and the risk of particular etiologies of dermatologic conditions. Future directions that were not accounted for in the present research include examining follow up consultations and their effect on patient outcomes as well as a detailed examination of the role of biopsy and culture in consultative services. Furthermore, exploring how consultations performed by other services (for example, infectious diseases) impact dermatology consultations would improve upon our understanding of the interactions of various services in the caring of a hospitalized cancer patient.

Conclusion

The findings in this study fill a gap in our understanding of the spectrum of skin conditions that affect inpatients with a primary cancer diagnosis, reinforcing the importance of oncodermatology collaboration, research, and education to optimize the management of hospitalized cancer patients, and in particular inpatients with hematologic cancers.

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Abbreviations

OR	odds ratio
CI	confidence interval
dAE	dermatologic adverse event
EGFR	epidermal growth factor receptor
MSK	Memorial Sloan Kettering Cancer Center

IQR	interquartile range
LOS	length of stay
SD	standard deviation
NOS	not otherwise specified

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Table I

Dermatology consultation pattern at MSK

		Dermatology Consultation		
Characteristic		No (N patients=11121)	Yes (N patients=412)	P value
<i>Patient characteristics</i>				
Age (years)				.006
	Median (IQR)	62 (51 – 71)	59.5 (49 – 69)	
	Range	0 – 100	1–87	
	N	11121	412	
Gender				.044
	Female	5664 (51%)	189 (46%)	
	Male	5457 (49%)	223 (54%)	
Primary cancer diagnosis				<.0001 ^a
	Brain	408 (4%)	24 (6%)	
	Breast	909 (8%)	34 (8%)	
	Gastrointestinal	3047 (27%)	36 (9%)	
	Genitourinary	1505 (14%)	33 (8%)	
	Gynecologic	925 (8%)	18 (4%)	
	Head and Neck	433 (4%)	12 (3%)	
	Leukemia	430 (4%)	111 (27%)	
	Lung	1292 (12%)	24 (6%)	
	Lymphoma	652 (6%)	68 (17%)	
	Multiple Myeloma	236 (2%)	16 (4%)	
	Other	702 (6%)	5 (1%)	
	Sarcoma	340 (3%)	19 (5%)	
	Skin	242 (2%)	12 (3%)	
<i>Outcome during admission</i>				
Died in hospital during admission				<.0001
	No	10861 (98%)	377 (91%)	
	Yes	260 (2%)	35 (9%)	
Length of stay (days)				<.0001
	Median (IQR)	5 (3 – 8)	11 (5 – 25)	
	Range	2 – 152	1 – 153	
	N	11121	410 ^b	

^aSignificant in a multivariable model that included age, gender, and primary cancer diagnosis

^b Admission and discharge dates were not available for 2 dermatology consultations

Table II

Comparison of characteristics between patients seen at a single versus multiple consultations

Characteristic	Strata	Single consultation (N=370, 90%)	Multiple consultations (N patients=42, 10%)	P value
Age (years)	Median (IQR)	60.5 (49 – 69)	56 (45 – 64)	.109
	Range	1–87	15 – 82	
	Mean (SD)		53.1 (16.3)	
Sex				.163
	Female	174 (47%)	15 (36%)	
	Male	196 (53%)	27 (64%)	
Number of consultations				
	2	-	27 (64%)	
	3	-	13 (31%)	
	4	-	2 (5%)	
Primary Cancer				<.001
	Brain	23 (6%)	1 (2%)	
	Breast	34 (9%)	0 (0%)	
	Gastrointestinal	36 (10%)	0 (0%)	
	Genitourinary	31 (8%)	2 (5%)	
	Gynecologic	18 (5%)	0 (0%)	
	Head and Neck	11 (3%)	1 (2%)	
	Leukemia	89 (24%)	23 (55%)	
	Lung	22 (6%)	2 (5%)	
	Lymphoma	56 (15%)	12 (29%)	
	Multiple	0 (0%)	2 (5%)	
	Multiple Myeloma	15 (4%)	1 (2%)	
	Other	5 (1%)	0 (0%)	
	Sarcoma	18 (5%)	0 (0%)	
	Skin	12 (3%)	0 (0%)	

Table III

Characteristics of dermatologic consultations

Characteristic	Strata	N consultations=471
Anticancer Treatment		
	Combination	79 (17%)
	Cytotoxic	135 (29%)
	Hormonal	10 (2%)
	Immunotherapy	18 (4%)
	Targeted	52 (11%)
	None	177 (38%)
Radiation		
	No	430 (91%)
	Yes	41 (9%)
Surgery		
	No	397 (84%)
	Yes	74 (16%)
Dermatologic Reason for Admission		
	No	353 (75%)
	Yes	118 (25%)
Referring Service Division		
	General Medicine	50 (11%)
	Hematology Oncology	206 (44%)
	Pediatrics	18 (4%)
	Solid Tumor Oncology	125 (27%)
	Surgery	72 (15%)

Table IV

Distribution of Dermatologic Diagnoses

Dermatologic Diagnosis	Subcategory	N diagnoses=645
Inflammatory		174 (27%)
	eczematous dermatitis	82 (13%)
	rash, other	30 (5%)
	lesion, other	16 (2%)
	urticarial reaction	9 (1%)
	graft-versus-host disease	7 (1%)
	miliaria	7 (1%)
	radiation dermatitis	7 (1%)
	acne	6 (1%)
	neutrophilic dermatosis	5 (1%)
	vasculitides	5 (1%)
Infection		156 (24%)
	viral	61 (9%)
	bacterial	48 (7%)
	fungal	25 (4%)
	infection, NOS	22 (3%)
Drug Reaction		111 (17%)
	chemotherapy	40 (6%)
	other drug/unspecified	34 (5%)
	antimicrobial	29 (4%)
	analgesic	8 (1%)
Drug Reaction vs Infection (viral exanthema)		14 (2%)
Lymphatic/Vascular Insufficiency Complication		69 (11%)
	edema	34 (5%)
	stasis dermatitis	14 (2%)
	vascular insufficiency complication, other	12 (2%)
	capillaritis	9 (1%)
Neoplasm		64 (10%)
	benign neoplasm	21 (3%)
	cutaneous lymphoma	18 (3%)
	cutaneous metastasis	13 (2%)
	leukemia cutis	9 (1%)
	primary skin cancer	3 (0%)
Ulcer/Wound		37 (6%)
Xerosis/Pruritus		20 (3%)