

DOI: 10.4274/gulhane.galenos.2021.26349
Gulhane Med J 2022;64:19-26



Dermatology consultations in patients with hematological and solid organ malignancies

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Date submitted:
25.08.2021

Date accepted:
04.12.2021

Online publication date:
15.03.2022

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Keywords: Dermatology, consultation, hematology, oncology, malignancy

ABSTRACT

Aims: Patients with hematological or solid organ malignancies are susceptible to various skin disorders. This study described the cutaneous problems related to the underlying diseases or their management in hematology and oncology inpatients.

Methods: In this retrospective study with a cross-sectional analysis, we examined the medical records of inpatients with hematologic or solid organ malignancy who consulted the dermatology department from January 2018 through March 2021. Sociodemographic characteristics, medical history and comorbidities, cancer type, and dermatological findings and diagnoses were noted. Patients who have consulted the outpatient clinic and those with inadequate medical records were excluded.

Results: The study included 200 patients (age, mean±standard deviation, minimum-maximum: 51.4±18.2, 18-89 years; female 51%). Most of the consultations were from the internal medicine clinic (26.4%), followed by the hematology and oncology clinics (12.5%). A quarter of the patients had acute myeloid leukemia, the most frequent disease among hematological malignancies. Breast cancer (7%) and testis cancer (7%) were the most common solid organ malignancies. The most common dermatological diagnoses were cutaneous infections (33.5%) and drug reactions (13.5%). Skin biopsies were performed in 19.5% (n=39) of the patients. The evaluation of the patient by a dermatologist for a cutaneous symptom or finding led to modifications of disease management in 67 patients (33.7%).

Conclusions: Dermatology consultations are frequently required in hematological or solid organ malignancies. A successful evaluation of skin manifestations in these patients may improve the quality of care in this vulnerable population.

Introduction

Hospitalized patients frequently need multidisciplinary care. Dermatologists may play a pivotal role in managing inpatients, usually more complicated and challenging than many outpatients (1). A study examining 591 dermatology consultations showed that 78% of the inpatients were misdiagnosed by non-dermatologists (2). Dermatology consultations change the diagnoses made by the primary team in more than 60% of the patients and affect the treatment plan of most (1,3-5). Despite some discrepancy among the published studies, the most frequent requesting service is internal medicine, while hematology and oncology are among the most common subspecialties (4,6).

However, dermatology is among the top five consultations requested from oncology clinics (7). Due to underlying diseases, chemotherapy, stem cell transplantation, and multi-drug treatments, immunosuppression makes this group prone to cutaneous conditions (7,8). Recently, there have been promising advances in cancer therapeutics with many new treatment agents, including immune checkpoint inhibitors, associated with cutaneous immune-related side effects (7-10). Therefore, there is an increasing need for closer collaboration between hematology, oncology, and dermatology departments (7,8).

Few studies have described the characteristics of skin findings in detail in hematology and oncology patients so far. In this study, we aimed to 1) categorize the frequent dermatological

diseases in hospitalized patients with malignancy, 2) analyze the role of dermatologists in diagnosing associated dermatological conditions, and 3) demonstrate the effect of dermatologists in the treatment strategies of patients.

Methods

This was a retrospective, cross-sectional study conducted using the medical records of patients diagnosed with hematologic and oncological malignancies who were referred to the dermatology clinic for cutaneous manifestations. The study included inpatient admissions between January 2018 and March 2021. Patients under the age of 18, not hospitalized, or with insufficient medical history were excluded. The study was approved by the University of Health Sciences Turkey, Gülhane Training and Research Hospital Ethics Board (decision no: 2021/123, date: 06.01.2022).

We used the data from the Department of Dermatology and Venereology of the University of Health Sciences Turkey, a tertiary referral care hospital that provides consultant services for inpatients and outpatients. Sociodemographic and medical information, including cancer characteristics (cancer type, current therapeutics) and dermatological findings, were collected from the electronic medical records and patient charts.

Cutaneous conditions evaluated

Cutaneous conditions were classified into ten groups according to etiology:

1. Cutaneous infections (viral eruption, cellulitis, herpes zoster, fungal infection, scabies),
2. Drug eruptions,
3. Inflammatory disorders (subtypes of dermatitis),
4. Malignant tumors (cutaneous metastasis or primary skin cancer),
5. Steroid-induced acneiform eruption,
6. Deep vein thrombosis and thrombophlebitis,
7. Chemotherapy skin side effects,
8. Xerosis and pruritus,
9. Graft-versus-host disease (GVHD) and,
10. Other skin conditions.

Skin biopsy results following the dermatologist's evaluation were recorded. Recommendations by the dermatologist and whether the consultation changed the patient's immediate treatment plan were also analyzed.

The accuracy of the prediagnoses, if any, specified by the primary care team was also evaluated.

Additionally, we evaluated the effect of Coronavirus disease-2019 (COVID-19) on dermatology consultations requested for hematology and oncology patients.

Statistical Analysis

Statistical analyses were performed by Statistical Package for the Social Sciences for Windows version 22.0 (IBM, Armonk, NY, USA). Categorical variables were presented by frequency and percentage. Normally distributed continuous variables were expressed as mean±standard deviation. Non-normally distributed continuous variables were expressed as median (interquartile ranges, minimum-maximum).

Results

Demographics

A total of 2120 inpatient referrals were made during the study period. Of these, 265 (12.5%) were from the hematology and oncology clinics. Dermatology consultations were ordered most commonly from the internal medicine clinic (26.4%), followed by the intensive care unit (9.5%) and surgical clinics (8.3%). Among the internal medicine clinics, the highest number of referrals were from the hematology and oncology clinics (12.5%), followed by rheumatology (6.5%) and nephrology (4.7%).

The number of total consultations requested by years was 42 in 2018 (21%), 45 in 2019 (22.5%), 81 in 2020 (40.5%), and 53 in the only first three months of 2021 (26.5%). About half of the consultations (48%) (n=96) were requested during the COVID-19 pandemic, corresponding to the last 12 months of the 39-month study period. Of the 265 hematology-oncology consultations requested in total, 65 were follow-up consultations of the same patients. Of these patients, 37.5% had at least one medical comorbidity (Table 1).

Characteristics of underlying malignancies

Various hematologic (n=113) or solid organ malignancies (n=87) were encountered (Table 1). Distant organ metastases were present by 7.5%. The overall mortality rate was 2% (n=4). Among the deceased patients, orolabial herpes (n=2), contact dermatitis, and cutaneous metastasis of testis cancer were the dermatological diagnoses following consultations. These patients died within one week of the consultation request.

Role of the dermatology consultation

In this study, 47 different dermatological diagnoses were made in 10 major disease categories. All consultations were evaluated within 8 h of the consultation request.

The most common diagnoses were cutaneous infections (33.5%) and drug eruptions (13.5%), followed by dermatitis (11.5%), cutaneous metastasis (7.5%) (Figure 1a, 1b), xerosis and pruritus (5.5%), steroid-induced acne (5%), deep vein thrombosis and thrombophlebitis (3%), chemotherapy skin side effects (3%) (Figure 1c, 1d), GVHD (2.5%), and miscellaneous skin disorders (11.5%) (Table 2).

Table 1. Demographic and clinical characteristics of the patients (n=200)	
Age, years, mean±standard deviation (minimum-maximum)	51.4±18.2 (18-89)
<30, mean (standard deviation)	36 (18)
30-49, mean (standard deviation)	59 (29.5)
50-65, mean (standard deviation)	54 (27)
>65, mean (standard deviation)	51 (25.5)
Sex (female/male)	98/102
Comorbidity (n=74)	n (%)
Hypertension	28 (14)
Diabetes mellitus	18 (9)
Cardiac disease	11 (5.5)
Benign prostate hypertrophy	6 (3)
Pulmonary disease	5 (2.5)
Thyroid disease	5 (2.5)
Psychiatric disorder	5 (2.5)
Hematologic malignancy (n=113)	n (%)
Acute myeloid leukemia	50 (25)
Multiple myeloma	18 (9)
Acute lymphoblastic leukemia	14 (7)
Non-Hodgkin lymphoma	14 (7)
B-cell lymphoma	4 (2)
Mantle cell lymphoma	4 (2)
Burkitt lymphoma	4 (2)
Other (chronic myeloid leukemia, intestinal T-cell lymphoma, large B-cell lymphoma, natural killer T-cell lymphoma, follicular lymphoma)	5 (25)
Solid organ malignancy (n=87)	n (%)
Breast	14 (7)
Testis	14 (7)
Colon	12 (6)
Lung	9 (4.5)
Pancreas	5 (2.5)
Malignant melanoma	4 (2)
Stomach	4 (2)
Other [Ewing sarcoma (n=3), ovarian cancer (n=3), glioblastoma multiforme (n=3), osteosarcoma, peripheral nerve sheath tumor, cholangiocellular cancer, renal cell cancer, osteosarcoma, liposarcoma, hepatoblastoma, hepatocellular cancer, bladder cancer, rectum cancer, peripheral nerve sheath tumor, malignant mesenchymal tumor, gastrointestinal stromal tumor, endometrium, cervix, unknown origin]	25 (12.5)

Drug reaction was the second most common diagnosis. Steven Johnson syndrome (SJS)-toxic epidermal necrolysis (TEN) overlap (Figure 1e) due to the use of phenytoin-valproic acid and fluconazole was observed in two patients with lung and bladder cancers, respectively. Urticarial drug reaction (n=1) and symmetrical drug-related intertriginous and flexural exanthema (n=1) were recorded following administration of ciprofloxacin and piperacillin-tazobactam, respectively. The use of multiple antibiotics (≥3 antibiotics simultaneously) was recorded in three patients diagnosed with fixed drug eruptions. In 8 (40%) patients with maculopapular drug eruptions (n=20), simultaneous dual broad-spectrum antibiotic use was recorded; a combination of

meropenem-teicoplanin was the most common suspicious dual-antibiotic (n=4). Meropenem (n=7), teicoplanin (n=5), piperacillin-tazobactam (n=3), and trimethoprim-sulfamethoxazole (n=3) were the most common individual suspicious antibiotics leading to a maculopapular (morbilliform) drug eruption. The majority (73.9%) of patients with maculopapular drug eruption had a hematological malignancy twice as common in patients with solid organ malignancies (13.3% vs. 5.7%).

Hematology and oncology services mentioned a suspicious diagnosis of their own in 34.5% (n=69) of dermatology consultations but no preliminary diagnosis in 65.5% of the patients. The dermatology team confirmed the preliminary



Figure 1. Cutaneous metastasis: **a)** A 64-year-old male patient with angiosarcoma and bone metastases. Purple-brown nodule, approximately 1*1 cm in size, on the medial side of the right knee. Histopathological examination confirmed angiosarcoma skin metastasis. **b)** A 22-year-old male patient was diagnosed with acute myeloid leukemia. Subcutaneous nodules are darker than normal skin, appearing on the trunk one month ago. The biopsy was compatible with leukemia cutis.

Acral peeling syndrome: **c, d).** A 76-year-old male patient diagnosed with colon cancer complained of peeling on the hands and feet after the 3rd course of capecitabine treatment. His symptoms were relieved with a potent topical steroid and moisturizer.

Steven Johnson Syndrome-toxic epidermal necrolysis overlap: **e)** A 68-year-old male patient was diagnosed with prostate cancer (2010) and lung cancer (2019). Fenotion was started due to brain metastases three weeks ago. Nikolsky signs positive areas with the involvement of more than 10% of the total body. In the early period, intravenous immunoglobulin was planned for the patient. And phenytoin, as well as suspicious other drugs, were stopped immediately

diagnosis by the hematologist or medical oncologist in 70.1% of 69 patients. The highest diagnostic accuracy was observed in GVHD and cutaneous side effects of cancer therapeutics (100%). However, stasis dermatitis was consulted as cellulitis in 30% of the cases, and 44.4% of the cutaneous metastases were mistaken for zona zoster or folliculitis. Steroid-induced acne, which can be observed in malignancy patients receiving high-dose steroids according to the treatment schedule, was the least accurately recognized dermatological diagnosis by primary physicians (Table 3).

Evaluation of the histopathological results

Histopathological examination was used in 19.5% (n=39) of the patients to confirm the dermatological diagnosis. Dermatology consultations led to changes in the medical management of 63 patients (31.5%) through the modification of antibiotic treatment (9%), current chemotherapy sessions (17.5%), or chemotherapeutic options and treatment plans (5%). Treatments recommended for the medical management of patients are listed in Table 4.

Discussion

In this study, the most common cutaneous disorder among dermatology inpatient consultations in hematology

and oncology clinics was cutaneous infections followed by drug eruptions. Since oncology and hematology inpatients are immunosuppressed and predisposed to neutropenia due to cancer therapeutics, they are more susceptible to mucocutaneous infections and drug reactions due to multiple drug use and prophylaxis schemes (8-13). Although GVHD (2.5%) and cutaneous side effects of chemotherapeutics (3%) have been commonly reported in previous studies (8,10-13), they were rarely observed in our study. The current study included only the patients consulted in the dermatology department; therefore, all inpatients in hematology and oncology clinics were not examined. Since our hospital is a tertiary referral center for bone marrow transplantation and cancer treatment, hematologists and oncologists might be more familiar with skin conditions specifically related to their specialties, such as GVHD and the side effects of chemotherapeutics. Therefore, they might have managed some other patients without the need for a dermatology consultation. The correct preliminary diagnoses for these two dermatological diseases also support our suggestion.

The most common diagnoses in our study were cutaneous infections. More than half of them did not relate to any significant risk of mortality and morbidity, such as localized fungal or bacterial infections. The most frequently observed subgroups were zona zoster, cellulitis, and tinea unguium. Interestingly,

Table 2. Dermatological diagnoses in hematology and oncology inpatients

Cutaneous infections (n=67), n (%)		
Viral	Herpes zoster	10 (7)
	Oral herpes	5 (2.5)
	Chicken pox	3 (1.5)
Bacterial	Cellulite	10 (6)
	Folliculitis	6 (3)
	Paronychia	3 (1.5)
Fungal	Tinea unguium	10 (5)
	Tinea pedis	6 (3)
	Pityriasis versicolor	5 (2.5)
	Tinea corporis	4 (2)
	Candidiasis	3 (1.5)
	Deep fungal (actinomyces)	1 (0.5)
Parasitic	Scabies	1 (0.5)
Drug eruptions (n=27), n (%)		
	Maculopapular	20 (10)
	Fixed drug	3 (1.5)
	SJS	2 (1)
	Urticarial	1 (0.5)
	Symmetrical drug-related intertriginous and flexural exanthema	1(0.5)
Dermatitis (n=23), n (%)		
	Contact dermatitis	7 (3.5)
	Seborrheic dermatitis	6 (3)
	Stasis dermatitis	5 (2.5)
	Perianal dermatitis	3 (1.5)
	Dermatitis (noted without specification)	2 (1)
Malignant skin tumors (n=19), n (%)		
Cutaneous metastasis	Acute myeloid leukemia	4 (2)
	Breast cancer	3 (1.5)
	Testis cancer	3 (1.5)
	Unknown origin	2 (1)
	Other (Burkitt lymphoma, intestinal T-cell lymphoma, lung cancer, angiosarcoma, colorectal)	5 (2.5)
Primary	Basal cell carcinoma	2 (1)
Steroid-induced acneiform eruption (n=10)		
Xerosis and accompanying pruritus (n=10)		
Deep vein thrombosis and thrombophlebitis (n=6)		
Cutaneous side effects of cancer therapeutics (n=6), n (%)		
	Acral peeling syndrome (capecitabine, cytarabine, bleomycin- etoposide-cisplatin, regorafenib)	3 (1.5)
	Palmar erythema (docetaxel)	2 (1)
	Nail discoloration (paclitaxel)	1 (0.5)
GVHD (n=5)		
Miliaria (n=2)		
Miscellaneous (n=25) (intertrigo, Still's disease, dystrophic calcification, amyloidosis, bullous pemphigoid, epidermal cyst, insect bite, vasculitis, stasis-related bulla, traumatic ecchymosis, acrochordon, leukocytoclastic vasculitis, terra firma forme dermatosis, petechiae secondary to thrombocytopenia). GVHD: Graft-versus-host disease, SJS: Steven Johnson syndrome		

Table 3. Diagnostic concordance and the influence of dermatology consultation

Cutaneous condition	Consulted with provisional diagnose/n	Diagnostic accuracy (%)*
Graft-versus-host disease	4/4	4/4 (100)
Cutaneous side effects of cancer therapeutics	5/6	5/5 (100)
Zona zoster	8/10	7/8 (87.5)
Tinea pedis and unguium	5/16	4/5 (80)
Cellulite	13/15	9/13 (69.2)
Drug eruption	14/27	9/14 (64.2)
Orolabial herpes	5/5	3/5 (60)
Cutaneous metastasis	9/19	5/9 (55.5)
Steroid-induced acneiform eruption	5/10	1/5 (20)

n: the total number of patients with that diagnosis. *Patients whose preliminary diagnosis by the physician was confirmed by the dermatologist / patients who were consulted with a preliminary diagnosis

Table 4. Treatments for medical management

Topical (n=145), n (%)		Systemic (n=78), n (%)	
Corticosteroids	55 (27.5)	Antihistamine drugs	26 (13)
Emollients	30 (15)	Antibiotics	19 (9.5)
Antibiotics	25 (12.5)	Antiviral	17 (8.5)
Antifungals	21 (10.5)	Corticosteroids	14 (7)
Acne treatments	10 (5)	Antifungal	6 (3)
Wet dressings	6 (3)		
Antivirals	3 (1.5)		

these infections are some of the essential topics of dermatology education in medical school, which could be better recognized by the primary team and primarily described in the consultation note. Nevertheless, the diagnostic accuracy of cellulitis was relatively low by the primary physicians. Stasis dermatitis was present approximately in one of every three patients consulted dermatology with the diagnoses of cellulitis. One study at two separate centers showed that 20-35% of patients admitted for cellulitis by the emergency department were mistakenly diagnosed as cellulitis by physicians other than dermatologists and infectious diseases specialists (14). Although stasis dermatitis is a clinical mimicked of cellulitis, bilateral, chronic, and non-tender erythema with usually long-standing pitting edema mainly indicates stasis dermatitis (1,15). A history of trauma in the affected area or accompanying tinea pedis or unguium with tenderness, warmth, swelling, and indistinct borders in a unilateral erythematous plaque, points to cellulitis. Additionally, rapid onset, presence of systemic symptoms such as fever, immunosuppression, and satisfactory response to antibiotics are findings in favor of cellulitis. However, in indistinguishable cases, Doppler ultrasonography could be considered (15,16). These observations suggest that postgraduate dermatology training programs help physicians better assess and manage patients with underlying malignancies and build more proper collaboration with dermatologists.

Drug reactions are another common dermatological condition with a higher risk of morbidity and mortality in patients with underlying malignancies. The frequency of adverse drug reactions in hematology consultations varies between 13 and 38% (8,17,18). In our study, drug reactions were recorded in 13.5% of 200 patients, and most of them were morbilliform drug eruptions (10%) in line with previous literature 9-17.3% (8,10,18). As in our study, most morbilliform drug reactions were uncomplicated conditions. Morbilliform or maculopapular drug eruptions usually present 1 to 2 weeks after initial exposure of the causative drug, may also show up sooner on rechallenge. Although most cases regress within 1-2 weeks, dermatology consultation is critical in confirming the diagnosis and excluding imitators such as viral exanthema seen in the immunosuppressive patient group (19,20). A dermatologist can help determine the suspected drug(s). More importantly, dermatologists may help to recognize the early signs of severe cutaneous drug reactions (SJS and TEN) such as mucosal involvement, skin tenderness, blistering, dusky red and coalescent macular exanthema, atypical target lesions, and Nikolsky sign (ready removal of the epidermis with slight unrelated pressure) (20,21). Therefore, dermatology consultations should be considered in the early period for patients with diffuse maculopapular eruptions.

The current study demonstrates the possible dermatological diagnoses encountered by physicians working with patients with

hematology and oncological malignancies. Although 47 different dermatological diagnoses were made in 10 main disease categories, most patients (72.5%) were managed with topical therapy, and only 39% required systemic medications. These data suggested that most skin conditions could be governed without aggressive treatments.

This study presents the 39-month experience of an advanced tertiary center. The last 12 months of the study period corresponds to the COVID-19 pandemic, which has rapidly affected the world and caused severe morbidity and mortality. While our center was mainly in charge of managing patients with COVID-19 infection in this period, hematology and oncology services were at the forefront of the departments that tried maintaining inpatient service properly. In this period, dermatology consultations are essential due to various skin manifestations of COVID-19 infections including urticarial, purpuric, erythema multiforme-like, chickenpox-like rash, acro-ischemia, chilblain-like eruptions, and pityriasis rosea like eruptions (22-25). Intense anxiety among patients and physicians and cutaneous side effects of several systemic medications are likely to increase dermatology consultations during the pandemic period. All these factors are potential causes of the increasing number of dermatology consultations in hematology and oncology inpatients during the pandemic period.

The retrospective design and lack of long-term follow-up are the main limitations of this study. The major strength is documenting a three-year experience of a large population from an advanced tertiary center.

Conclusion

In conclusion, the current study indicates that dermatology inpatient consultations of hematological or solid organ malignancies play an essential role in determining skin manifestations associated with underlying malignancy or treatment of the disease. A close collaboration between hematologists, oncologists, and dermatologists helps manage patients with underlying malignancies appropriately.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, Gülhane Training and Research Hospital Ethics Board (decision no: 2021/123, date: 06.01.2022).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: P.E., S.N.Ç., G.A., Design: P.E., S.N.Ç., G.A., Data Collection or Processing: P.E., S.N.Ç., G.A., Analysis or Interpretation: P.E., S.N.Ç., G.A., Literature Search: P.E., S.N.Ç., G.A., Writing: P.E., S.N.Ç., G.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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