Observational Study

Morphological Evaluation of Micronutrient Deficiency Dermatoses in Hospitalized Patients: A Cross-Sectional Study

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Abstract

INTRODUCTION While micronutrient deficiencies are associated with classic dermatologic manifestations, there may be associated cutaneous lesions which are nonspecific. Failure to recognize heterogeneous nutritional dermatoses may result in the underdiagnosis of nutritional disease. **METHODS** A descriptive, cross-sectional analysis of 531 inpatients with dermatological conditions and laboratory confirmed micronutrient deficiencies were queried from a single institution healthcare database. Demographics and hospital outcomes were extracted from hospital records. Morphologies and locations of cutaneous lesions were extracted using a formal template from consult notes. **RESULTS** The average affected patient was overweight (mean BMI of 31.3 ±10.4 kg/m2), and less than 30% had combined protein-calorie malnutrition. Psychiatric disease (n=195, 36.7%) and chronic liver disease (n=105, 19.2%) were frequent comorbid conditions. Overall, nonspecific cutaneous presentations (n=252, 47.5%) were more common than classic presentations (n=140, 26.4%) among patients with vitamin C, A, zinc, and/or B-complex deficiencies. **CONCLUSIONS** Physicians should maintain a high index of clinical suspicion for micronutrient deficiencies, even in the absence of classic disease associations to facilitate laboratory testing and early intervention.

Keywords: General dermatology, medical dermatology, vitamin deficiency, nutrient deficiency, clinical research, micronutrient deficiency dermatoses, inpatient dermatology

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INTRODUCTION

Nutritional deficiencies are common and can be associated with classic dermatologic manifestations; however, nonspecific presentations in vitamin and mineral micronutrient deficiencies are under-recognized, resulting in delayed treatment and poor patient outcomes.[1,2] Underserved patients, those with psychiatric disorders, substance use disorders, hyper-catabolic states, chronic inflammatory states, and gastrointestinal disease have a higher risk of developing nutrient deficiency, even in developed countries.[3–5]

Additionally, previous studies have demonstrated an association between patients with micronutrient-associated skin disease and increased lengths of hospitalization, higher frequencies of readmission, and higher mortality rates. [6,7] Although associated with significant morbidity, nutritional deficiencies can be addressed when promptly identified. [8–10] Unfortunately, no standardized approach for hospital screening of malnutrition based on skin disease exists.[8] In this cross-sectional study, we describe cutaneous morphologies associated with micronutrient deficiency and identify patient risk factors associated with nutritional disease.

METHODS

Patients were queried from The Ohio State University Wexner Medical Center Information Warehouse. Inclusion criteria included: 1) an admission date between January 1, 2011 and December 31, 2017; 2) admission to the OSU main hospital or an ancillary hospital of the medical center; 3) an International Classification of Diseases (ICD9CM/10)-coded skin disease during hospitalization; and 4) laboratory evidence of micronutrient deficiencies. Our final cohort was composed of patients with confirmed vitamin A, B1, B6, C, and/or zinc deficiencies. B6 deficiencies were infrequent, but occurred concomitantly with vitamin B1 deficiency, so these were grouped as "B-complex" deficiencies. There were additional patients with copper, vitamin E, vitamin B2, or biotin deficiencies for further study. B3 deficiency was excluded, given high test variability which does not adequately test full body stores and the limited availability of tests for B3 urinary biproduct excretion.[11]

Consult notes were reviewed for demographic information, discharge diagnosis, discharge disposition, one-year readmission rate, and comorbidities. Cutaneous lesions were grouped into "classic" and "nonspecific" categories. Classic presentations were defined based on expert review, standard dermatology textbooks, and literature review analysis (Table 1).[1, 3-5,8] Classic findings present alongside more than one deficiency were categorized separately respective to each deficiency. Patients were initially identified using laboratory test confirmation. Subsequently, hospital consultation and progress documentation were reviewed using a standardized template of classic morphologies and appearances. Cutaneous morphologies that did not group into a nutrient deficiency were categorized as "nonspecific" (Table 3). "Poor wound healing" was differentiated from ulcers based on a consult note's morphological description of "poorly healing" wounds without mention of a persistent ulceration. JMP Pro statistical software (2019, SAS institute/15.2.0) was used for data analysis. χ^2 and Fisher's exact test were utilized to analyze the association of risk factors, chronic comorbidities, and micronutrient deficiencies. Odds ratio (OR) was utilized to analyze the proportions of nonspecific vs. classic cutaneous presentations. All continuous data are represented as mean ± standard deviation.

The study was conducted in accordance with IRB guidelines and standard research protections.

Table 1. *Classic cutaneous, mucosal, and ocular manifestations of nutrient deficiency.*

Vitamin Deficiency	**Classic Cutaneous Manifestations**
Vitamin A	Follicular papules/Follicular Scale Blurry Vision/Bitot's spots
Vitamin B-complex	Angular cheilitis Waxy Skin Red, thickened tongue Itching/burning sensation Soreness of lips/tongue/gums

Vitamin Deficiency	Classic Cutaneous Manifestations
Vitamin C	Ulcers, Poor wound healing Perifollicular hemorrhagic papules Corkscrew hair Gingival hyperplasia Purpura/Ecchymosis
Zinc	Angular cheilitis Periorificial rash Paronychia Alopecia Eczematous/Psoriasiform plaques Poor wound healing

RESULTS

Demographics

Of the 531 patients included in the study, the mean age was 56.4 ± 16.3 years with a mean body mass index (BMI) of 31.3 ±10.4 kg/m2. 274 (51.6%) patients were female (Table 2).

Table 2. *Demographics, Comorbidities, and Outcomes.*

Demographics and Comorbidities					
Vitamin deficiency (n)	B-complex (n=98)	Zinc (n=135)	Vitamin A (n=26)	Vitamin C (n=163)	Multinutrient (n=109)
Age at index hospitalization (years), mean (SD)	58.6 (16.4)	56.4 (16.4)	52.9 (20.1)	56.8 (14.8)	53.4 (16.6)
Female, % Male, %	52 (53.1%) 46 (46.9%)	71 (52.6%) 64 (47.4%)	16 (61.5%) 10 (38.5%)	75 (46.0%) 88 (54.0%)	60 (55.0%) 49 (45.0%)
BMI, mean (SD)	29.5 (8.9)	31.3 (10.3)	30.4 (7.6)	32.1 (9.2)	58.8 (291)
Protein Calorie Malnutrition	13 (13.3%)	42 (31.1%)	3 (11.5%)	23 (14.1%)	41 (37.6%)
Chronic Liver Disease	8 (8.2%)	35 (25.9%)	8 (30.8%)	35 (21.5%)	16 (14.7%)
Chronic Kidney Disease	15 (15.3%)	17 (12.6%)	4 (15.4%)	39 (24%)	15 (13.8%)
Malabsorption syndrome	12 (12.2%)	7 (5.2%)	1 (3.9%)	9 (5.5%)	7 (6.4%)
Bariatric Surgery	5 (5.1%)	9 (6.7%)	1 (3.9%)	7 (4.3%)	6 (5.5%)
Psychiatric Disorder	39 (39.9)	5 (33.3%)	15 (57.7%)	53 (32.5%)	43 (39.1%)

Alcoholism	7 (7.1%)	15 (11.1%)	3 (11.5%)	26 (16.0%)	9 (8.2%)
IV Drug use	3 (3.1%)	5 (3.7%)	3 (11.5%)	7 (4.3%)	1 (0.9%)
Cancer	30 (30.6%)	31 (23.0%)	9 (34.6%)	42 (25.8%)	28 (25.5%)
Top 5 Diagnoses at Discharge					
Sepsis/Bacteremia	12 (12.2%)	30 (22.2%)	3 (11.5%)	31 (19.0%)	28 (25.5%)
Cardiovascular Disease	5 (5.1%)	9 (6.7%)	0 (0.0%)	19 (11.7%)	8 (7.3%)
GI Disease	8 (8.2%)	12 (8.9%)	5 (19.2%)	15 (9.2%)	7 (6.4%)
Neurologic Disorder	15 (15.3%)	11 (8.2%)	2 (7.7%)	13 (8.0%)	5 (4.6%)
Noninfectious skin condition	16 (16.3%)	21 (15.6%)	5 (19.2%)	18 (11.0%)	29 (26.4%)
Outcomes					
Inpatient Mortality	7 (7.1%)	20 (14.8%)	0 (0.0%)	13 (8.0%)	8 (7.3%)
1 year readmission	44 (44.9%)	59 (43.7%)	15 (57.7%)	84 (51.5%)	52 (47.3%)
Discharge Disposition					
Home or Self Care	47 (48.5%)	44 (32.6%)	15 (57.7%)	75 (46.0%)	35 (31.8%)
Home Health Services	14 (14.4%)	16 (11.9%)	3 (11.5%)	23 (14.1%)	21 (19.1%)
Skilled Nursing Facility	14 (14.4%)	35 (25.9%)	6 (23.1%)	30 (18.4%)	24 (21.8%)

Distribution of Vitamin Deficiencies

Of the micronutrients evaluated in our cohort (vitamins C, A, zinc, and B-complex), the associated cutaneous findings were most commonly located on the extremities (n=331, 62.3%) and trunk (n=161, 30.3%). Vitamin C deficiency was most common (n=163, 30.7%), followed by zinc (n= 135, 25.4%), B-complex (n=98, 18.5%), and vitamin A (n=26, 4.9%). 109 patients (20.5%) had multinutrient deficiencies (≥2), of which vitamin A/zinc (n=24, 4.5%) and vitamin C/zinc (n=41, 7.7%) were most frequent.

Associated Comorbidities

Concurrent protein-calorie malnutrition was documented among 122 (22.9%) patients. Psychiatric disease (n=195, 36.7%), cancer (n=140, 26.4%), and chronic liver disease (n=102, 19.2%) were common chronic comorbidities associated with micronutrient deficiencies (Table 2).

Classic and Nonspecific Dermatologic Presentations

In our cohort, 140 (26.4%) patients with nutrient deficiencies had classic presentations, and 252 (47.5%) patients had nonspecific morphologic documentation (Table 3). 139 (26.1%) patients had no rashes documented. Ulcers (n=108, 20.3%) were the most common nonspecific morphology documented among patients with nutrient deficiency, followed by erosions/crust (n=82, 15.4%), desquamation (n=57, 10.7%), and hypo/hyperpigmentation (n=52, 9.8%) (Table 4).

Table 3. *Primary and secondary lesions and morphologies associated with nutrient deficiency: This table includes patients with multinutrient deficiencies; Patients may be represented in more than one category.*[1]

	Classic *N Column%*	**Nonspecific** *N Column%*	**Odds Ratio** (95% CI)	**p-value**
Vitamin A (n=70)	13 (18.5%)	38 (54.2%)	5.2 CI [2.4, 11.2]	p<0.0001
Vitamin B-complex (n=131)	20 (15.3%)	33 (25.2%)	1.9 CI [1.0, 3.5]	p=0.020
Vitamin C (n=234)	51 (21.8%)	99 (42.3%)	2.6 CI [1.8, 3.9]	p<0.0001
Zinc (n=223)	56 (25.1%)	82 (36.7%)	1.7 CI [1.5, 2.6]	p=0.004

Table 4. *Nonspecific morphologies associated with nutrient deficiency.*

	N	**%**
Ulcers	108	(20.3%)
Erosions/Crust	82	(15.4%)
Desquamation	57	(10.7%)
Hypo/Hyperpigmentation	52	(9.8%)
Pustular	36	(6.8%)

Vitamin C Deficiency

Nonspecific presentations (42.3%) were more common than classic presentations (21.8%) among patients with vitamin C deficiency (OR = 2.63, 95% CI: [1.76, 3.94], p<0.0001). Of the classic disease associations, purpura/ecchymosis (n=30, 12.8%) were frequent, and documented "poor wound healing", gingival hyperplasia and friability, perifollicular hemorrhagic papules, and corkscrew hair were rarely documented (Table 3).

Zinc Deficiency

Among patients with zinc deficiency, characteristic "eczematous or psoriasiform" plaques (n=15, 6.7%) were common. Additional classic morphologies such as periorificial rashes, paronychia, alopecia, and documented "poor wound healing" also occurred. Overall, nonspecific presentations (36.7%) were more frequent than classic presentations (25.1%) among patients with zinc deficiency (OR=1.73, CI: [1.54, 2.60], p=0.004).

B-complex Deficiency

Nonspecific presentations were more frequent than classic presentations among patients with B-complex deficiencies (25.2% vs 15.3%, OR=1.875, CI: [1.01, 3.47], p=0.020). Documented "itching/burning" sensation (n=10, 7.6%) was the most common classic disease association. Additional classic manifestations such as angular cheilitis were documented infrequently.

Vitamin A Deficiency

Among patients with vitamin A deficiency, characteristic follicular scale was common (n=6, 8.5%). Overall, nonspecific cutaneous presentations were more common than classic presentations among patients with vitamin A deficiencies (54.2% vs 18.5%, OR=5.23 CI: [2.43, 11.18], p<0.0001).

Discharge and Follow-Up

A total of 388 different primary discharge diagnoses were grouped into 19 categories, e.g., cardiovascular disease, sepsis, etc. (Table 2). Using this classification method, the top 5 diagnoses at discharge were sepsis/bacteremia (n=104, 20.0%), non-infectious skin conditions (n=89, 16.8%), gastrointestinal disease (n=47, 8.9%), neurologic disorders (n=46, 8.7%) and cardiovascular disease (n=41, 7.7%). Patients hospitalized with neurologic disorders had B-complex deficiencies more often than the other micronutrient deficiencies identified (n=15, 15.3%). Cardiovascular disease was more common among patients with vitamin C deficiency (n=19, 11.7%) than other micronutrient deficiencies. Thirty-one patients with vitamin C deficiency (19.0%) and 30 patients with zinc deficiency (22.2%) had sepsis. Forty-eight patients died during hospitalization, with the highest inpatient mortality occurring in patients with zinc deficiency (n=20, 14.8%) (Table 2). Following hospitalization, 216 patients (40.7%) requiring self-care were discharged home, while 109 (20.5%) patients were discharged to a skilled nursing facility, and 77 patients (14.5%) were discharged with home health care services. Half of patients were readmitted within 1 year of discharge (47.6%). The frequency of readmission was generally similar across the various deficiencies.

DISCUSSION

Nearly one third of the U.S. population is at risk of deficiency in at least one vitamin.[9] Our study aims to increase awareness of the cutaneous spectrum associated with micronutrient deficiency and identify associated patient risk factors.

Patients at Risk for Micronutrient Deficiency

In this cohort of 531 inpatients with a laboratory-confirmed micronutrient deficiency, chronic liver disease, alcoholism, chronic kidney disease, psychiatric disorders, and cancer were common comorbid conditions. These documented high-risk patient categories for nutritional deficiency are consistent with other studies suggesting malnutrition is primarily related to chronic illness, malabsorption, and restrictive dietary habits in developed countries.[9, 11-14] Notably, psychiatric illness was the most common comorbidity present in more than one third of the cohort, possibly secondary to restrictive intake and concomitant substance use disorders; however, it is notable that certain medications such as anti-epileptics put patients at risk for B-vitamin deficiencies. [15,16]

Chronic liver disease is associated with protein-calorie malnutrition in hospitalized patients and portends a poor prognosis. [17] Similarly, chronic liver disease was present in nearly one-fourth of the cohort, appearing most frequently among patients with vitamin A and zinc deficiencies. Chronic liver disease is also a risk factor for zinc deficiency, as approximately 80% of plasma zinc is bound to the liver plasma protein albumin.[18,19] Similarly, vitamin A is primarily stored hepatically.[20]

In our cohort, concurrent micronutrient and macronutrient deficiency was frequent. Previous studies have estimated the prevalence of protein-energy malnutrition in hospitalized patients at 6%.[5] In our cohort, 23% of patients had protein-energy malnutrition (defined by serum albumin <3.5 g/dL). Consistent with previous literature, protein-energy malnutrition was common among patients with zinc deficiency, which may support theories that oxidative stressors are among the potential drivers of malnutrition in hospitalized patients.[8,21,22] Although albumin and pre-albumin are often used as biomarkers of protein-malnutrition, [23] nearly 80% of our cohort did not have protein-energy malnutrition. Screening for albumin and pre-albumin alone is insufficient to diagnose the complexity of nutritional disease. Together, these data emphasize the importance for dermatologists to recognize specific patient populations with comorbidities at risk for these micronutrient deficiencies.

Multinutrient Deficiency

Multinutrient deficiency was common in our cohort and exhibited frequent overlap with vitamin A/zinc deficiency and vitamin C/zinc deficiency. A cross-sectional study evaluating the associations of zinc, vitamin A, and vitamin C deficiency found an inverse relationship with leptin concentrations in obese women. [24] In our cohort, obesity was a frequent factor, which may support previous literature suggesting that vitamin C and zinc deficiency play a role in fat deposition.[24] Additionally, dietary and lifestyle habits associated with obesity may lead to an

imbalance in other micronutrients. Thus, nutritional deficiency should not only be suspected in emaciated or underweight patients. [25,26]

Cutaneous Presentations of Micronutrient Deficiency

In our cohort, classic cutaneous presentations were frequent (n=140, 26.4%). However, nonspecific presentations were more commonly associated with micronutrient deficiency (n=252, 47.5%). Nearly one-fourth of the cohort had ulcerative lesions, and overall, the rate of nonspecific cutaneous morphologies was more frequent than classic morphologies among patients with vitamin C (42.3% vs 21.8%), vitamin A (54.2% vs 18.5%), B-complex (25.2% vs 15.3%), and zinc (36.7% vs. 25.1%) deficiencies. In addition to the eczematous or psoriasiform plaques commonly attributed to zinc deficiency,[3-5,8] nonspecific morphologies such as pustules (n=22, 9.8%) and desquamation (n=32, 14.4%) were also documented in our cohort.

In our cohort, 60% of documented cases of hypo/hyperpigmentation were associated with vitamin C deficiency (n=31) (including vitamin C-associated multinutrient deficiencies). Vitamin C administration alone has reversed hyperpigmentation secondary to Addison's disease, suggesting a direct correlation between vitamin C deficiency and skin pigmentation.[27-29] Further, nearly half of the patients who died during hospitalization had zinc deficiency (n=20, 13.8%), which was substantially higher than other associated deficiencies.

Previous literature suggests these nonspecific lesions may be progressive morphologies secondary to untreated nutrient deficiency.[3-5,8] This may suggest that dermatoses which do not favor accessible areas, such as the trunk and extremities, may be underrecognized in hospitalized patients.

Although classic skin lesions can be diagnostic, cutaneous manifestations associated with nutrient deficiency are frequently overlapping and nonspecific.

LIMITATIONS

A major limitation to this study is the testing modalities used. Classic B-complex dermatoses such as pellagra could not be differentiated, because the standard test for B3 does not test full-body stores, instead focusing on recent ingestion patterns. Similarly, there were insufficient patients to comprehensively evaluate additional micronutrients (copper, vitamin E, B2, B9, and B12 deficiencies). Additionally, inflammation is known to alter the validity of several laboratory test results. Further, most of our cohort was hospitalized for a primary condition and secondarily diagnosed with micronutrient deficiency. Thus, some cutaneous morphologies may be underreported, as dermatology consultations in hospitalized patients are often focal and area-specific. Although our analysis is of a single center, we note that this study was substantially larger than similar studies performed on hospitalized inpatients in the United States.[7, 8]

CONCLUSIONS

Cutaneous disease may be the first manifestation of underlying nutritional deficiency, and malnutrition is associated with significant healthcare utilization.[9, 31] This study highlights the relatively high incidence of nonspecific cutaneous morphologies documented among patients with nutrient deficiency, as well as reinforcing the typical risk factors associated with micronutrient deficiency. Our data suggest screening with albumin, prealbumin, or underweight body habitus is insufficient to identify patients with nutritional disease. Dermatologists should be aware that micronutrient deficiencies are not localized to the developing world and be prepared to test for nutrient deficiency, especially in hospitalized patients with high-risk comorbidities.

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Abbreviations

OR	Odds Ratio
BMI	Body Mass Index

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