A Multifaceted Examination of Cutaneous Disease Associated with Oncologic Conditions: Atypical Post-Radiation Vascular Proliferation, Cutaneous Neoplasms in Lynch Syndrome patients, Non-Melanoma Skin Cancer in Children, and Case Studies of Rare Cutaneous Eruptions.

by

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Abstract

A wide variety of skin conditions can arise in cancer patients, whether from cancer therapy, underlying genetic syndromes, paraneoplastic processes, or immunosuppression. This thesis examines five skin conditions that typically arise in oncologic patients: atypical post-radiation vascular proliferation (APRVP), skin neoplasms in Lynch syndrome, nonmelanoma skin cancers in pediatric patients, dermatomyositis in a patient with EGFR exon 20 mutation non-small cell lung cancer, and atypical erythema multiforme in a patient after bone marrow transplant. The first three studies are multi-institutional retrospective reviews that characterize the demographic and clinical characteristics of the conditions. The last two studies are case reports that suggest a possible pathogenetic mechanism and highlight the importance of recognizing atypical presentations in cancer patients. Through these five studies, this thesis provides insight into risk factors, preventative screening, management, and prognosis of rare cutaneous conditions that may enhance dermatologic care of patients with cancer.

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Glossary

AK: actinic keratosis
APRVP: atypical post-radiation vascular proliferation
AVL: atypical vascular lesion
BCC: basal cell carcinoma
BMT: bone marrow transplant
CMV: cytomegalovirus
DM: dermatomyositis
EBV: Epstein-Barr virus
EGFR: epidermal growth factor receptor
EM: erythema multiforme
ESR: erythrocyte sedimentation rate
GVHD: graft-vs-host disease
HDM: hypomyopathic dermatomyositis
HNPCC: hereditary non-polyposis colorectal cancer
HSV: herpes simplex virus
LS: Lynch syndrome
MRI: magnetic resonance imaging
NMSC: non-melanoma skin cancer
NSCLC: non-small cell lung cancer
PCR: polymerase chain reaction
PUVA: psoralen and ultraviolet A
SCC: squamous cell carcinoma
VZV: varicella zoster virus
WBC: white blood cell

Introduction

Cancer patients are susceptible to a wide variety of dermatologic diseases, either as a manifestation of cancer therapy toxicity, underlying genetic syndromes, paraneoplastic processes, or immunosuppression. These dermatologic diseases may manifest in unique ways, and management of these diseases may require novel approaches in the setting of cancer and immunosuppression (1).

This thesis examines a range of dermatologic conditions that can occur in the setting of cancer. The first study is a retrospective review of atypical post-radiation vascular proliferation (APRVP), a lesion that occurs years after radiation therapy, usually to the breast for breast cancer (2,3). While APRVP is generally thought to be benign, there may be a small chance it can transform into cutaneous angiosarcoma (2,4,5). Current studies on this condition are limited to small cohorts of patients, and thus, the risk factors and transformation rate to angiosarcoma are not clear. The purpose of this study was to examine the clinical and demographic characteristics of APRVP, study the natural progression of the disease, and compare the outcomes in patients who underwent excision vs. monitoring.

The second study is a cross-sectional study of Lynch syndrome patients who have cutaneous neoplasms. Lynch syndrome, also known as hereditary non-polyposis colorectal cancer (HNPCC), is an autosomal dominant condition due to mutations in DNA mismatch repair genes (6). Lynch syndrome is traditionally associated with colorectal cancer, but in the Muir-Torre variant of Lynch syndrome, patients also have an increased risk of developing sebaceous

carcinomas and keratoacanthomas (7,8). However, the association between Lynch syndrome and other types of skin cancer are not well established, and thus, the dermatologic screening guidelines for these patients are unclear. The purpose of this study was to characterize cutaneous neoplasms in Lynch syndrome patients and determine a genotype-phenotype correlation between Lynch syndrome mutations and types of skin neoplasms.

The third study is an examination of pediatric patients with non-melanoma skin cancers (NMSC). NMSCs in pediatric patients are rare and usually develop in the context of radiation therapy, chemotherapy, or a genetic condition (9,10). However, there are some patients who develop NMSCs without any of these risk factors (9). This study compares the demographic and clinical characteristics of pediatric patients who develop NMSCs with predisposing genetic and iatrogenic risk factors, with those who do not have risk factors. In doing so, this study aims to shed light on pediatric patients who develop NMSCs without identifiable risk factors.

The fourth and fifth chapters are case reports of rare cutaneous eruptions in the setting of cancer therapy. The first case is a patient with epidermal growth factor receptor (EGFR) exon 20 mutation non-small cell lung cancer who developed hypomyopathic dermatomyositis, an uncommon form of dermatomyositis characterized by skin findings and subclinical elevations in muscle enzymes. This case explores possible pathogenetic mechanisms of this paraneoplastic process and sheds light on key diagnostic features of dermatomyositis in patients with cancer. The second case is a patient with B cell lymphoma, status post bone marrow transplant, who developed an atypical presentation of erythema multiforme, thought initially to be graft vs. host

disease. This case highlights how concurrent diagnoses can cause atypical presentations of skin conditions, and the importance of recognizing unique skin findings in cancer patients.

In characterizing five cutaneous conditions that may arise in patients with cancer, this thesis takes a multifaceted examination of oncodermatology and provides insight into pathophysiology, risk factors, and prognosis of rare cutaneous conditions.

Characteristics of atypical post-radiation vascular proliferation: a retrospective review of 193 patients

Introduction

Atypical post-radiation vascular proliferations (APRVPs) or atypical vascular lesions (AVLs) were first described by Fineberg and Rosen in 1994 as lesions distinct from malignant angiosarcomas that typically follow a benign course. As with cutaneous angiosarcomas, APRVPs are thought to be sequelae of radiation therapy and have been increasingly diagnosed over the last two decades (2,3).

Angiosarcoma and APRVP can be difficult to distinguish clinically and histologically. Previous studies have suggested that APRVPs affect patients who are 10 years younger, have a three-year shorter duration from radiation to onset, and present as smaller and more discrete lesions than angiosarcomas (2,11,12). Histologically, APRVPs tend to have anastomosing vascular channels within the dermis with focal dissection of dermal collagen (12). They are usually confined to the dermis without cytologic atypia, multilayering, mitoses, necrosis, or blood lakes (2). However, these histopathologic characteristics alone are not diagnostic due to morphologic overlap with cutaneous angiosarcoma.

APRVP and angiosarcomas may be on the same morphologic continuum (2) or they may be two separate entities, given the high amplification of *MYC* and *FLT4* in angiosarcoma, but not usually appreciated in atypical vascular lesions (13,14). It is still unclear whether or not there is potential for APRVPs to transform into angiosarcoma, and what the putative rates and timeline would be (2,4,5). Due to the uncertainty of natural progression, the optimal management of

APRVPs has not been established. In addition, while the histopathology of APRVPs has been well described, descriptions of the demographic and clinical characteristics of APRVP remain limited.

We sought to conduct a large, multi-institutional review of APRVP to: (1) examine the demographic and clinical characteristics of patients with APRVP, (2) determine the rate and timeline of angiosarcoma diagnosis after APRVP diagnosis, and (3) compare outcomes of APRVP patients who underwent surgical excision versus active monitoring and surveillance.

Methods

Study Design, Setting, and Participants

This study was approved by the Partners Healthcare Institutional Review Board in Boston, MA. Patients were identified from electronic health records at Brigham and Women's Hospital, Dana Farber Cancer Institute, and Massachusetts General Hospital using free text search of "atypical post-radiation vascular proliferation" in pathology notes. Patients were identified between January 1, 1988 to December 8, 2018. Cases were included if the patient had a histopathologic diagnosis of APRVP. Patients were excluded if they were diagnosed with secondary cutaneous angiosarcoma concurrently with, or prior to, their diagnosis of APRVP, or if patients had no history of radiation exposure. Patients were defined as having APRVP excised versus monitored if they had pathology or clinic notes documenting the excision or active monitoring.

Data Collection

Medical records of patients with APRVP were reviewed for patient characteristics, features of primary malignancy, clinical features of the lesion (i.e. anatomic site, size of lesion, morphology, secondary features, number of lesions, and symptoms), comorbidities, treatment, outcomes, and whether or not the lesion was subsequently diagnosed as angiosarcoma.

Statistical Analysis

Descriptive statistics were conducted to summarize patient characteristics. Normality assumption was checked for continuous variables, and mean or median, depending on the variable distribution, was reported. Categorical variables were summarized as proportions and percentages. Where there was missing data, percentages were provided with the denominator excluding the missing cases. Patients were divided by management option (excision vs. monitoring) and comparisons were performed using a Fisher exact test or Chi-square test, depending on sample size, for categorical variables, and Wilcoxon rank sum test or t-test, depending on normality, for continuous variables. Two-sided tests with p-values less than 0.05 considered significant were used. Where there was a statistically significant difference in follow-up time, outcomes analysis at 980 days was performed, based on our cohort's timeline for recurrence and subsequent angiosarcoma diagnosis. Statistical analyses were performed on SPSS version 24 (IBM Corp).

Results

Patient characteristics

Our initial search yielded 254 patients, of which 196 (77.2%) patients had atypical post-radiation vascular proliferation as either a single diagnosis or prior to a diagnosis of secondary angiosarcoma. Fifty-eight patients were excluded because they had an initial diagnosis of secondary angiosarcoma. Nine of those patients (15.5%) had a concurrent diagnosis of APRVP, while forty-nine patients (84.4%) had a subsequent diagnosis of APRVP. Three patients were excluded because they did not have a history of radiation exposure. 193 patients were ultimately included in the analysis (Figure 1).

Ninety-eight percent (190/193) of patients were women, with a mean age of 61.3 (range 28 to 92) at APRVP diagnosis (Table 1). Ninety-four percent (178/189) of the patients were white, and 4.9% (4/82) of patients were current smokers. Eighty-eight percent (143/163) of the patients had primary breast malignancy, though a spectrum of cancers were represented, including lymphoma, lung cancer, vulvar or anal squamous cell cancer, and sarcomas (Table 1). For the 15 patients with data available on radiation dosage, the median radiation dosage was 50.4 Gy (range 45-64 Gy). The median time from radiation to APRVP was 6 years (range 1-40 years).

Follow-up outside of a pathologic diagnosis of APRVP was available for 100 of the 193 patients. Twenty-one percent (21/100) of patients had radiation-associated lymphedema and 21% (21/100) of patients had other documented complications of radiation, such as cardiopulmonary restrictive disease, hypothyroidism, infection, or chronic radiation dermatitis (Table 1). Eighteen percent (18/100) of patients had other cancers besides the primary cancer that preceded the development of APRVP. Twenty-five percent (25/100) of patients had recurrent primary cancers, with 92% (23/25) of these patients having the recurrence prior to their development of APRVP. Twenty-six

percent (26/100) of the patients had more than one biopsy before a diagnosis of APRVP was confirmed.

Fifteen patients received genetic testing, and of those patients, two (13.3%) had *BRCA1* mutations, two (13.3%) had *BRCA2*, five (33.3%) had a variant of unknown significance, and six (40.0%) had no detected mutations (Table 1).

APRVP characteristics

Eighty-five percent (164/193) of APRVP lesions were found on the breast, though other locations, such as the axilla, back, abdomen, and groin, were also sites of APRVP (Table 2). Sixty-eight percent (55/81) of patients presented with single lesions.

Of lesions with clinical measurements described in the medical record, 84.2% (32/38) were less than 1 cm (range: 1 mm to 9 cm). The larger lesions tended to be pink plaques with induration or swelling. Of note, six lesions were found incidentally during pathology after breast reconstruction with no mention of overlying skin changes in the medical record.

Clinically, there was varied presentation of APRVP (Figure 2). 35.4% (34/96) of lesions were described as papules, 21.9% (21/96) as plaques, and 17.7% (17/96) as patches. Induration and telangiectasias were commonly described secondary features. Eight APRVPs were found on surgical scars, two were complicated by infections, and one had concomitant squamous cell carcinoma pathology.

Most lesions were asymptomatic, though pain and pruritus were described in 6 and 3 patients, respectively (Table 2). Discharge, ranging from serous to yellow to bloody, was another characteristic described in 5 patients.

Outcomes

Median follow-up time, as defined as the time between APRVP diagnosis to the last clinical encounter in the medical record system, was 3.2 years, with the longest follow-up being 14.8 years (Table 1). Forty-seven percent (43/91) of patients with APRVP had their lesions excised and 52.7% (48/91) underwent clinical monitoring alone. For nine out of the 100 patients, there was no explicit information in the medical record as to whether the lesion was excised or monitored.

Three percent (3/100) of patients had a subsequent diagnosis of angiosarcoma, with a median time of 229 days (range: 54-235 days). All three lesions were in women with a primary malignancy of breast cancer. Twenty percent (20/100) of patients had subsequent APRVP diagnosed by biopsy or clinical appearance, with a median time to recurrence being 392 days (range 27-1955 days). Seventy-seven percent (77/100) of the lesions remained stable.

Ten percent (10/100) of patients were deceased at the end of the study, 6 of whom passed away because of their primary cancer, 1 from cardiac arrest, and 3 from unknown causes. Median time to death was 2.3 years (range: 0.02-8.2 years). Follow-up was available for only one of the three patients who developed angiosarcoma. This patient had no recurrence and was alive at the end of our study, which was 8.97 years after the patient's diagnosis of angiosarcoma.

Comparison of excision versus monitoring

Patients who had their APRVPs excised were diagnosed 2.8 years earlier than those with APRVPs monitored (median date: 4/18/12 vs. 12/13/14, respectively, p = 0.001; Table 2), though there was no difference in follow-up time. There was also no difference in age at APRVP diagnosis, race, age at primary malignancy, APRVP size, type of primary lesion, lesion number, or outcomes between the two groups. In both groups, one patient a subsequent diagnosis of angiosarcoma. For one patient, it was not clear whether or not the lesion was fully excised or monitored so she was excluded from this analysis.

Discussion

This study of 193 patients is the largest study to our knowledge on atypical vascular proliferations and sheds light on key features of this disease that may aid clinicians in diagnosing and managing patients with APRVP. The demographic profile of our cohort is consistent with prior studies: elderly, Caucasian, and strong female predominance. Our mean age of APRVP diagnosis, 61.3 years, and median time from radiation to development of APRVP, 6 years, is consistent with prior smaller studies (2,4). APRVP may be associated with cumulative radiation exposure, as 25% of patients had recurrent primary cancer and radiation therapy prior to their diagnosis of APRVP.

As with prior studies, most of our patients had primary breast malignancies with APRVPs appearing in the chest area. Three patients with APRVP of the breast were excluded from

analysis because they did not have a history of radiation exposure. However, two of these patients had a history of breast cancer and one had idiopathic chronic lymphedema of the bilateral breasts. Taken together, this suggests that radiation may only play one role in the development of atypical vascular lesions. The breast may be an especially common location for APRVP development because of the volume of irradiated skin, properties of breast tissue, and synergism between radiation and chemotherapy (2). Interestingly, connective tissue malignancies (i.e. sarcomas) were common primary cancers for non-breast APRVPs, suggesting that mesenchymal growth leading to sarcomas may have a common pathway with vascular proliferation.

Clinically, APRVPs presented most commonly as asymptomatic papules less than 1 cm in diameter. Indurated plaques, purpuric patches, and edematous breasts were also observed. In a single patient, multiple morphologies of APRVP may be seen, suggesting that APRVP has a spectrum of clinical morphologies similar to the varied histopathologic findings – ranging from superficial lymphatic proliferations to complex lymphatic and capillary vascular lesions – that have been described (4).

APRVPs may also be associated with scarring, infection, or skin cancer, manifesting in line with *locus minoris resistentiae* (15). APRVPs are typically asymptomatic, but pain, pruritus, and discharge may be observed. APRVPs may also be waxing and waning. The cause of this is unknown, but may reflect transitory impaired lymphatic drainage after radiotherapy, and may actually represent a precursor to persistent APRVP (16). Longer term studies are needed to understand the progression of these evanescent lesions.

Previous studies have recommended complete excision of APRVPs (2,17,18), though there has been a trend towards more conservative clinical monitoring of the lesions as anecdotal reports of longer-term follow-up without associated angiosarcomatous transformation have emerged (4,19). This is reflected in our study, as patients undergoing APRVP excision were diagnosed in earlier years than those who were monitored, suggesting a shift in prevailing management. Subgroup analysis of patients with excision versus monitoring revealed no difference in outcomes, though continued longer-term follow-up is warranted. There may be selection bias in these results as more clinically worrisome lesions may have been more likely to be excised. At our institution, we currently recommend clinical monitoring for most patients with APRVP after a shared discussion of risks and benefits with patients.

Our study corroborates previous literature that APRVP typically behaves as a benign lesion. Our recurrence rate of 20% is consistent with the 20% recurrence rate in Gengler et al. (19), though as mentioned in previous literature, these new lesions may not be true recurrences, but new lesions in the same irradiated field due to the field-effect phenomenon (20), or residual lesions. As such, field monitoring is crucial. We found that 3% (3/100) of our patients had a subsequent diagnosis of angiosarcoma, which is lower than a previously reported angiosarcoma transformation rate of 6.3% (2/32) (4). This may be due to the chance, given small sample sizes, or different patient population, rates of excision, or follow-up time. The short duration we observed between APRVP and angiosarcoma diagnosis suggests that there may be either mischaracterization of initial pathology, concurrent disease processes, or rapid evolution of

APRVP into angiosarcoma. As such, close clinical follow-up especially within the first two years of diagnosis of APRVP are most warranted.

Our study was limited by its retrospective nature and missing data. Outcomes need to be interpreted with caution as the median follow-up time was short, patients may have been lost to follow-up, or patients may have received care at different institutions.

Future investigations correlating histopathology findings with disease and demographic features in these patients may yield additional clinicopathologic insights regarding APRVP – particularly given the heterogeneous pathologic findings described in the literature – and better inform prognostic recommendations.

Our analysis of 193 patients with APRVP lends additional clinical insights into the limited understanding of these rare neoplasms. Regular dermatologic examinations post-radiation are crucial, though stable-appearing APRVPs may not need to be excised. Once APRVP is diagnosed, close follow-up and low threshold to re-biopsy rapidly changing lesions may aid in early angiosarcoma diagnosis.

Characterizing the spectrum of cutaneous neoplasms in individuals with Lynch syndrome

Introduction

Lynch syndrome (LS), or hereditary non-polyposis colorectal cancer (HNPCC), is an autosomal dominant disorder caused by mutations in DNA mismatch repair genes, namely *MLH1, MSH2, MSH6, PMS2,* and *EPCAM* (6). Lynch syndrome predisposes patients to colorectal cancer and extracolonic cancers, such as gastric, pancreatic, and endometrial cancer (21). Skin cancer represents 3-5% of extracolonic cancers (22), and sebaceous neoplasms and keratoacanthomas are uniquely associated with Lynch syndrome in what is known as the Muir-Torre variant (7,8). Approximately 5 to 9% of LS individuals have the Muir-Torre variant (7,23), and patients with sebaceous carcinoma have a 43% increased risk of a second malignancy compared with the general population (24). Thus, the occurrence of skin cancer in LS patients may be an important predictor of other types of cancers.

Besides sebaceous neoplasms and keratoacanthomas, other cutaneous neoplasms have also been observed in Lynch syndrome carriers (25). However, the association has not been well established, and the screening guidelines for LS patients without the Muir-Torre variant are still unclear (23). The objective of this study was to characterize cutaneous neoplasms found in Lynch syndrome and determine a genotype-phenotype correlation between the type of LS mutation and type of skin neoplasm. In doing so, this study aims to better inform dermatologic screening guidelines for patients with LS.

Methods

Study Design, Setting, and Participants

This study was approved by the Dana Farber Cancer Institute Institutional Review Board in Boston, MA. We conducted a retrospective analysis of patients with Lynch syndrome in the Lynch syndrome registry at Dana-Farber Cancer Institute (DFCI), Boston, MA. Patients were included if they had genetically confirmed Lynch syndrome (*MLH1, MSH2, MSH6, PMS2,* or *EPCAM* mutations), and self-reported or medically documented cutaneous neoplasms. Patients were excluded if they did not have genetic confirmation of Lynch syndrome.

Data Collection

Medical records of patients with LS were reviewed for demographic characteristics (race, gender, age), genetic mutation, types of cancers, and corresponding age.

Statistical Analysis

Descriptive statistics were used to analyze the spectrum of cutaneous neoplasms. Fisher's exact test was used to assess bivariate associations between skin neoplasm and specific LS genes. Odds ratios summarized the degree of association. Two-sided tests were conducted with p-values less than 0.05 considered significant. Missing data were excluded from analysis. Statistical analyses were performed using Stata version 15 (StataCorp).

Results

Patient demographic characteristics

There were a total of 976 individuals, from 532 families, in the Lynch syndrome registry (Figure 3). Of those, 126 (12.9%) Lynch syndrome carriers, from 113 families, had a history of skin neoplasms (Figure 3). 42% (53/126) of these patients were male and 4% (5/126) of patients were non-white. The median age was 66.7 (range 33.5-98.1) (Table 3).

Patient clinical characteristics

Of the 126 patients, a total of 271 cutaneous neoplasms were analyzed (Table 3). Only 126/271 (46.5%) of cutaneous neoplasms were classically associated with Lynch syndrome (keratoacanthoma and sebaceous neoplasms); other observed cutaneous neoplasms included squamous cell carcinoma (n=61), basal cell carcinoma (n= 45), melanoma (n= 23), Merkel cell carcinoma (n= 3), trichoblastoma (n= 1), and unspecified (n = 12).

Most skin neoplasms (66.9%) were located on the face/head (Figure 4). 35.7% (45/126) of patients had multiple cutaneous neoplasms and 33.3% (42/126) had multiple histologic types of cutaneous neoplasms.

Of the 98 subjects for whom age data were available, median age at first cutaneous neoplasm was 50 years (range 25-73) (Table 3). 76.2% (96/126) of Lynch syndrome carriers with a cutaneous neoplasm had a history of visceral malignancy as well, 21.2% (14/66; 30 individuals had missing age data for cutaneous and/or visceral malignancy) of whom were diagnosed with cutaneous neoplasm before their visceral malignancy.

Genotype-Phenotype correlation

Lynch syndrome carriers with *MSH2* mutations were significantly more likely to have any cutaneous neoplasm (OR 2.22, 95% CI 1.53-3.25). Among Lynch syndrome carriers with cutaneous neoplasms, there were significant associations between *PMS2* carriers and basal cell carcinoma (OR 8.8, 95% CI 2.6-29.5), and *MSH2* carriers and sebaceous neoplasms (OR 3.1, 95% CI 1.5-6.4) on bivariate analysis. There was no association between genotype and melanoma or squamous neoplasms (squamous cell carcinoma and keratoacanthomas).

Discussion

This study found that 12.9% of LS carriers in our cohort had a history of skin neoplasm, which is higher than the 8.2% reported previously in literature (23). This difference may be because the previous study only examined malignant neoplasms, whereas our study looked at both benign and malignant neoplasms (23). Our study also suggests that cutaneous neoplasms beyond classic Lynch-associated keratoacanthomas and sebaceous neoplasms are common in individuals with Lynch syndrome. Fewer than half (47%) of the cutaneous neoplasms in our study were classically associated with LS.

Regular dermatologic visits for Lynch syndrome carriers should begin at an early age as patients can develop cutaneous neoplasms as early as 25 years old. Most patients in our cohort (76%) had a visceral malignancy, and of those patients, 21% had a cutaneous neoplasm that preceded their visceral malignancy. This suggests that skin findings may be the first presentation of LS.

Sebaceous neoplasms are commonly found around the eye region, but in patients with the Muir-Torre variant, they can often occur on the trunk (24). In our study, most skin neoplasms (67%) were found on the face/head, though there were certainly sebaceous neoplasms on the trunk.

This study was limited in that there was a small sample size that may not be generalizable, particularly since only 4% of patients were not white. Given the retrospective nature of this study, it is difficult to determine cause and effect. Furthermore, there may have been recall bias and incomplete data, leading to skewed results in our analysis.

In the future, analysis of skin biopsies can help ascertain whether or not the skin cancers have loss of LS-associated protein expression or microsatellite instability, implying a causal effect of LS. We would also like to examine characteristics of LS patients without skin neoplasms and compare that with those who do. Finally, a comparison of LS skin neoplasm prevalence to that of the general population will help elucidate any increased risk that LS confers on patients. Previous studies have suggested that LS patients have a 12-fold increased risk at 60 years old of developing SCC and sebaceous carcinoma compared with the general Dutch population (23). However, the increased risk of other skin neoplasms, like melanoma and basal cell carcinoma, is unknown.

Overall, patients with LS exhibit a wide range of cutaneous neoplasms, beyond the typical keratoacanthoma and sebaceous neoplasms. Screening of cutaneous neoplasms in LS patients should start early, even before the onset of visceral malignancies.

Characteristics of non-melanoma skin cancer in children without identifiable risk factors

Introduction

Nonmelanoma skin cancer (NMSC) is rare in healthy children and young adults, and thus, has been poorly characterized (10,26–30). Recently, we described a multi-center cohort of patients with NMSC and found significant associations with both predisposing genetic conditions and iatrogenic exposures (9). Within this cohort, we also identified a subset of patients with no identifiable risk factors.

The primary objective of this study was to characterize demographic and clinical features of children and young adults with NMSC without identifiable risk factors. We also sought to identify differences between NMSC patients without identifiable risk factors and those with predisposing genetic conditions or iatrogenic exposures.

Methods

This multi-center retrospective cohort study was approved by the institutional review boards at Dana-Farber Cancer Institute (Protocol #15-156) and ten other institutions. Patients were included if they were: 1) diagnosed with NMSC including squamous cell carcinoma (SCC) or basal cell carcinoma (BCC), 2) younger than 20 years of age upon initial histopathologic diagnosis of NMSC, and 3) diagnosed between January 1, 1995 and June 30, 2016. Patients were excluded if there was no clinical information in the medical record.

Medical records were reviewed, and anonymized data was entered into RedCap software. We defined patients without identifiable risk factors as those without predisposing genetic conditions, predisposing skin lesions, and/or iatrogenic risk factors.

Descriptive analyses were performed to summarize patient demographics and clinical features. Patients were divided into the following categories: 1) no identifiable risk factors, 2) one or more iatrogenic risk factors, and 3) one or more predisposing conditions/skin lesions (see Table 4 for definitions). Since there were patients who had both iatrogenic and predisposing skin conditions/lesions, two analyses were conducted—one that included the overlapping group and one that did not. Tests of association were performed using Fisher's exact test for binary factors or Wilcoxon rank-sum test for continuous factors.

Results

Of 124 patients who met inclusion criteria, 37 (29.8%) had no identifiable risk factors, 21 (16.9%) had iatrogenic risk factors, 51 (41.1%) had predisposing conditions/skin lesions, and 15 (12.1%) had both predisposing conditions and iatrogenic risk factors. Analysis including and excluding the patients who had both predisposing conditions and iatrogenic risk factors yielded similar statistical results; thus, the data presented represent risk factor groups that do not overlap (n = 109; Table 4).

Demographics

Patients without identifiable risk factors were significantly older than those with predisposing conditions (median age: 15 [range 4.6-19.8] vs. 11 [range 0.9-19.4], p = 0.002; Table 4, Figure 5). There was no difference in gender, race, Fitzpatrick skin type, and geographic location between risk factor groups (Table 4).

Clinical characteristics

Thirty-two percent (12/37) of patients without identifiable risk factors had SCC, and 70% (26/37) had BCC (Table 4). The proportion of patients with each skin cancer type was not significantly different between risk factor groups. Forty-four percent (16/36) of patients without risk factors had skin cancers in intermittently or non-sun-exposed areas. This was not significantly different between risk factor groups (Table 4).

Patients without identifiable risk factors had fewer skin cancers at initial diagnosis than those with predisposing skin conditions/lesions (median: 1 [range 1-3] vs. 1 [range 1-30]; p = 0.0003; Figure 6). Only 3% (1/37) of patients without identifiable risk factors had actinic keratosis (AK), compared with 29% (6/21) of patients with iatrogenic risk factors and 20% (10/51) of patients with predisposing skin conditions (p = 0.007 and 0.02, respectively) (Table 4).

Five percent (2/37) of patients had subsequent skin cancers after the initial diagnosis, compared with 29% (6/21) of patients with iatrogenic risk factors and 65% (33/51) of patients with predisposing skin conditions/lesions (p = 0.02; p<0.0001, respectively). These patients also had fewer total skin cancers (median: 1 [range 1-7]) than those with iatrogenic (median: 1 [range 1-

6], $p = 0.002$) or predisposing skin conditions/lesions (median: 3 [range 1-126], $p < 0.0001$) (Figure 6).

9% (2/22) of patients without identifiable risk factors had a known family history of NMSC, and both patients had BCC. There was no difference in family history of NMSC between risk factor groups (Table 4).

Access to dermatologic care

The median time from onset of skin cancer to diagnosis was nine months (range 1.1-72 months). 87% (26/30) of patients were evaluated by a dermatologist for their initial skin cancer, and 36% (5/14) had been examined by a dermatologist prior to developing skin cancer (Table 4).

Survival outcomes

Of those with data, all (34/34) patients were alive at the end of our study (Table 4).

Discussion

This retrospective multi-center study spanning more than 20 years identified 37 out of 124 patients diagnosed with NMSC at < 20 years of age without identifiable risk factors. We found that this cohort presented at a later age with a lower skin cancer burden and incidence of concomitant actinic damage than those with iatrogenic or other predisposing risk factors. There were no patients in this cohort who had more than three initial skin cancers, or were younger

than four years of age at presentation. Only one of the 37 patients had evidence of actinic damage.

Prior to this study, cases of children diagnosed with NMSC without identifiable risk factors have been reported anecdotally and without rigorous evaluation of the patient's risk factor history (26,31–33). In a literature review of 107 children with idiopathic BCC, the median age of onset was 13 years, two years younger than our cohort's median age of 15 years (26). Eighteen percent of children had subsequent skin cancers, compared with our cohort's 5% (26). These differences may be attributed to the different inclusion criteria, especially the risk factors examined. Consistent with our study, idiopathic BCC has been more commonly reported than idiopathic SCC in children (26,33); the most common location for NMSCs is the head (26); and there are often delays in diagnosis because of low index of suspicion (26). In general, most patients respond well to surgical excision, consistent with the outcomes in our study (26,29,32,33).

Limitations of this study include retrospective design and small sample size, despite the 21-year period of review. The pathogenesis underlying skin tumorigenesis in these patients is unknown. While chronic sun exposure poses a major behavioral risk factor in adults, it is unlikely to be a major contributor to NMSC in children. Instead, there may be genetic variants or iatrogenic exposures that have not yet been identified; furthermore, some patients may have been mosaic for genetic conditions (34,35). Future tissue immunophenotyping and gene analysis may help elucidate causation and pathogenesis.

Overall, our study suggests that pediatric NMSC patients without identifiable risk factors have a milder phenotype with fewer subsequent skin cancers than those with iatrogenic or predisposing conditions. As such, these patients may be counseled on a good overall prognosis. Conversely, patients who present at less than four years of age, have more than three initial skin cancers, or have concomitant actinic damage should be examined closely for contributing factors including iatrogenic exposures and predisposing conditions or skin lesions. All patients with NMSC should receive regular skin exams and perform diligent sun protection to decrease the burden of disease.

Paraneoplastic hypomyopathic dermatomyositis associated with EGFR exon-20 insertion non-small cell lung cancer: a case report

Case Presentation

An 82-year-old woman with metastatic non-small cell lung cancer positive for EGFR exon 20 insertion presented with a pruritic rash on the chest, back, arms, and face for 3 years. She reported a 10-year history of pruritus and prior skin biopsies suggesting a hypersensitivity rash or lichen planus. Previous treatments had included topical betamethasone, psoralen and UV light therapy (PUVA), and oral gabapentin with some relief. Eight months prior, the patient was diagnosed with lung adenocarcinoma with spine involvement and was started on carboplatin and pemetrexed. Her pruritus improved with cancer treatment, but her skin eruption worsened. Due to cancer progression, she was due to start a new chemotherapy regimen, and was sent to dermatology for pretreatment evaluation of her rash. She endorsed shortness of breath, but denied muscle weakness, myalgias, dysphagia, arthritis, or fevers. She noted that her rash worsened with sun exposure.

On exam, the patient had confluent, photodistributed pebbly violaceous erythema of the upper chest, arms, and shawl distribution (Fig. 7). She had violaceous periorbital erythema and edema bilaterally and centrofacial erythema with nasolabial fold involvement. Diffuse scalp erythema and scaling were present. Her dorsal and palmar hands, thighs, and nailbeds were without lesions. Muscle strength was normal and symmetric.

Labs were notable for elevated aldolase, creatine kinase, lactate dehydrogenase, aminotransferases, and normal antinuclear antibody. Skin biopsy revealed interface dermatitis,

epidermal maturation disarray, and microvascular ectasia, consistent with dermatomyositis (Fig. 8). Serial ECGs revealed no significant changes. She was diagnosed with hypomyopathic dermatomyositis (DM).

Discussion

Hypomyopathic DM (HDM) is rare, affecting 2-3% of DM patients, and characterized by skin and muscle involvement without clinical muscle weakness (36). HDM may manifest as a paraneoplastic phenomenon. While HDM has been described in patients with lung cancer, hypomyopathic dermatomyositis has not been previously described in a patient with EGFR exon 20 insertion, a mutation found in up to 10% of EGFR mutated lung cancers, making the cancers insensitive to classical EGFR tyrosine kinase inhibitors (37).

One postulated mechanism relating DM and certain underlying cancers is autoantibody cross reactivity. EGFR mutations may have a particular association with dermatomyositis, as both EGFR mutations and DM may be associated with specific HLA alleles and the exon 20 EGFR mutation may be particularly immunogenic (38,39).

Treatment of paraneoplastic HDM should be directed at the underlying malignancy. Patients should be monitored for the development of clinical muscle weakness, interstitial lung disease, and cardiac disease. Cardiac involvement, in particular, can affect up to 72% of DM patients, with 46% of patients dying from heart disease (40). Heart abnormalities may be subclinical; use of cardiac MRI or other imaging may facilitate diagnosis (40).

This case highlights a unique association between NSCLC, exon 20 EGFR mutation, and hypomyopathic dermatomyositis. Recognizing this may shed light on a possible pathogenetic mechanism of paraneoplastic DM. Clinically, physicians should suspect dermatomyositis in patients with persistent itch and skin changes, particularly in the extensor and sun-distributed areas, keeping in mind that clinical muscle weakness may not always be present. In doing so, proper workup and treatment can be pursued in a timely fashion.

Atypical cutaneous targetoid lesions after bone marrow transplant: a case report

Introduction

Graft-versus-host disease (GVHD) and erythema multiforme (EM) are two cutaneous conditions that may both manifest after bone marrow transplantation (BMT). In GVHD, donor T lymphocytes attack host cells, while in EM, autoreactive T cells cause inflammation in the individual's own tissues. Acute cutaneous GVHD may have multiple morphologies, but is most typically characterized by generalized erythematous macules, while EM classically manifests with target lesions. Both can be pruritic and demonstrate mucosal involvement.

We report a case of idiopathic EM with a component of GVHD that resulted in atypical morphology of the cutaneous lesions. This case discusses the pathogenesis of EM and GVHD, how to distinguish the two entities, and highlights the uniqueness of this patient's presentation.

Case presentation

A 69-year-old man with esophageal EBV-positive diffuse large B cell lymphoma status post allogeneic bone marrow transplant (BMT) five months prior presented to his oncologist with three days of maculopapular rash that started on his legs and spread to his arms and trunk in the setting of tacrolimus taper. Dosing of tacrolimus was reduced from 2 mg BID to 1 mg BID one week prior to the onset of the rash. The rash was burning and pruritic, with no fevers or systemic symptoms. The patient had not started new medications and was compliant with his current

medications, which included acyclovir prophylaxis and gabapentin. He was diagnosed with grade 1 GVHD based on clinical findings and started on oral prednisone 80 mg daily.

Ten days later, he presented to dermatology for rash progression while on prednisone. On exam, there were numerous pink, raised ovoid lesions with targetoid appearance and lightly depressed dusky centers, some with central erosions or small vesicles, on the dorsal hands, extremities, chest, back, abdomen, ears, and legs (Figure 9). Oropharynx, groin, and conjunctiva were clear.

Skin biopsy showed vacuolar interface dermatitis with florid dyskeratosis (Figure 10). Labs were notable for elevated erythrocyte sedimentation rate (ESR) of 29 mm/hr (normal 0-12), white blood cell (WBC) count 4,920/uL (baseline 1,500), hemoglobin of 12.4 g/dL (normal 13.5-18), platelets of 86,000/uL (normal 150,000-450,000), and normal liver function tests. Serologies for acute HSV, CMV, VZV, and EBV IgM were negative.

GVHD and EM can be difficult to distinguish because of shared characteristics. Both GVHD and EM may show necrotic keratinocytes, dermal inflammatory infiltrate, and subepidermal clefting on histopathology. Morphologically, GVHD may manifest as EM-like targetoid lesions (41,42). One helpful distinction is that GVHD is often associated with systemic symptoms, such as fever and diarrhea, and abnormal findings on relevant clinical and laboratory investigations, such as jaundice, transaminitis, pancytopenia, and marrow aplasia, while EM is not (42).

The patient had an atypical appearance of EM due to ear involvement, scaling, and florid dyskeratosis on histology. The patient may have had a component of acute inflammation as the graft cells were summoned to the skin in the event due to the EM eruption; cutaneous eruptions

can trigger GVHD. However, given the absence of systemic findings or laboratory abnormalities commonly found in GVHD, as well as the pronounced targetoid morphology and confirmatory histopathology, our patient's ultimate diagnosis was EM.

The patient was initially started on topical tacrolimus 0.1% ointment, which was switched to clobetasol propionate 0.05% ointment when he complained of burning and tingling of his hands and feet. He continued his valacyclovir and gradually tapered his prednisone from 80 mg to 20 mg in a stepwise manner within one month as his rash improved.

At follow-up dermatology appointment one month later, the patient showed significant improvement with only two residual and fading violaceous papules on his shoulder and knee, without signs of new lesions. Two months later, the patient was admitted to the hospital for *Pneumocystis carinii* pneumonia and required intubation. The patient passed away shortly thereafter.

Discussion

Erythema multiforme is an acute mucocutaneous eruption, characterized by target lesions. It is commonly related to underlying infections, such as herpes simplex virus, but in up to 58% of cases, the etiology is unknown (43). Our patient had no obvious inciting factors for EM, such as drugs, infections, or autoimmune disease, suggesting that his EM was most likely idiopathic. There have been reported associations of non-Hodgkin's lymphoma with EM (44), as atypical

cancer cells could participate in the hypersensitivity reaction (45). However, our patient had already undergone BMT and was without signs of active malignancy.

Despite our patient having negative HSV viral PCR and being on prophylactic acyclovir, HSV is important to consider in patients following BMT. HSV genetic fragments may localize in stem cells, which can deliver the fragments to the skin on differentiation (46). Reactivated HSV can also increase the risk of GVHD through its ability to stimulate T-cell proliferation (47). Thus, underlying viral infections triggering both EM and GVHD can cause atypical cutaneous reactions seen post-BMT.

Our patient's case was unique in that his erythema multiforme was atypical, given the scaling, substantial ear involvement, and florid apoptotic keratinocytes on histology. This atypical morphology is most likely due to a component of GVHD as graft cells were recruited to the sites of inflammation. To distinguish between GVHD and EM, it is important to consider that GVHD may be associated with systemic symptoms, such as transaminitis, fever, and pancytopenia, and GVHD tends to occur 30 days post-transplant. GVHD may rarely also occur in a skin-limited manner. EM can occur at any time and is more likely accompanied by pruritus (42). Histologically, GVHD and EM may be affected by the medications used post-BMT. For example, immunosuppressive agents, such as the tacrolimus that our patient was on, target T lymphocytes so the inflammatory reaction in GVHD may be predominantly macrophages (48).

This case highlights the importance of recognizing atypical eruptions in patients post-BMT. Because of similarities between GVHD and EM, cutaneous reactions post-BMT may fall under a

larger umbrella or spectrum of EM-reactive dermatoses (46,47). The timing of our patient's eruption coinciding with the tapering of immunosuppression initially raised the possibility of GVHD, but the atypical morphology appreciated by his oncologist triggered a dermatology evaluation. The differential for post-transplant cutaneous eruptions should be broad to avoid missing correct diagnoses and appropriate treatment.

Discussion and Conclusion

Cutaneous manifestations in cancer patients are varied and ever-increasing as the armamentarium for cancer is expanding. This thesis consists of five studies on cutaneous eruptions seen in oncologic patients.

The study examining atypical post-radiation vascular proliferations found that the demographic characteristics in this large cohort of 193 patients was elderly and Caucasian, with a strong female predominance. Most patients had primary breast malignancies, though sarcomas were the second most common primary malignancy, suggesting a common mesenchymal pathway for sarcomas and atypical vascular proliferations. Clinically, APRVPs most commonly present as asymptomatic papules less than 1 cm in diameter and can be waxing and waning. There were no differences in outcomes in excision vs. monitoring. Thirty-four percent of patients had recurrent APRVP, and 3% of lesions were later diagnosed as angiosarcoma with a median time of 229 days after initial diagnosis.

The study of skin neoplasms in Lynch syndrome patients found that there are many skin neoplasms beyond keratoacanthomas and sebaceous adenomas, which are traditionally associated with Lynch syndrome. Cutaneous neoplasms can occur before a visceral malignancy and the earliest age at which a skin neoplasm was diagnosed in our cohort was 25 years. As such, screening of skin cancers should occur early and frequently in patients with Lynch syndrome and a wide variety of skin neoplasms should be considered.

In pediatric patients, NMSCs are often associated with cancer, as patients with previous chemotherapy and radiation therapy are more likely to develop NMSCs. In our multicenter study, we found that close to 30% of patients did not have risk factors, such as cancer, to predispose them to NMSCs. These patients without risk factors were more likely to present with fewer skin cancers and no evidence of actinic damage than those with iatrogenic and/or predisposing conditions. While all patients with NMSC should receive regular skin exams and perform diligent sun protection, physicians can counsel these patients on the likelihood of low skin cancer burden and good prognosis.

In our first case study, we describe a patient with EGFR exon 20 mutation NSCLC who developed hypomyopathic dermatomyositis, suggesting a possible link between the particularly immunogenic lung cancer and the rare form of dermatomyositis. In the second case study, we report a patient with an atypical presentation of erythema multiforme after bone marrow transplant. The EM was particularly scaly, suggesting a component of GVHD along with the EM.

These studies provided in-depth examinations of rare cutaneous conditions, usually found in the setting of cancer. However, these studies were limited in that they were retrospective, introducing the possibility of bias from missing data. Furthermore, these conditions are rare so the sample sizes were relatively small, despite the long time periods of review and their multicenter nature.

Future work

Future studies are needed to correlate histopathologic findings with disease and demographic features in APRVP, skin neoplasms in Lynch syndrome, and NMSCs in pediatric patients. In particular, understanding the relationship of lymphatic type vs. vascular type APRVP and their prognoses can better inform management. In the Lynch syndrome study, an analysis of protein expression and microsatellite instability in skin neoplasms will better inform the extent of causal influence of LS mutations. In NMSCs in pediatric patients, histopathologic studies may shed light on the pathogenetic mechanisms of NMSCs in patients with and without risk factors. Finally, larger studies of all of these conditions will elucidate a better understanding of the disease.

Summary

This thesis provided a multifaceted examination of cutaneous conditions in oncologic patients. The conditions covered were atypical post-radiation vascular proliferation, skin neoplasms in Lynch syndrome patients, non-melanoma skin cancers in pediatric patients, dermatomyositis in a patient with EGFR exon 20 mutation NSCLC, and atypical erythema multiforme in a patient who recently underwent a bone marrow transplant. Using retrospective methods and case studies, this thesis characterized the demographic and clinical features of these rare cutaneous conditions to better inform screening and management guidelines.

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Tables and Figures

APRVP

Figure 1**: Flowchart of included patients**

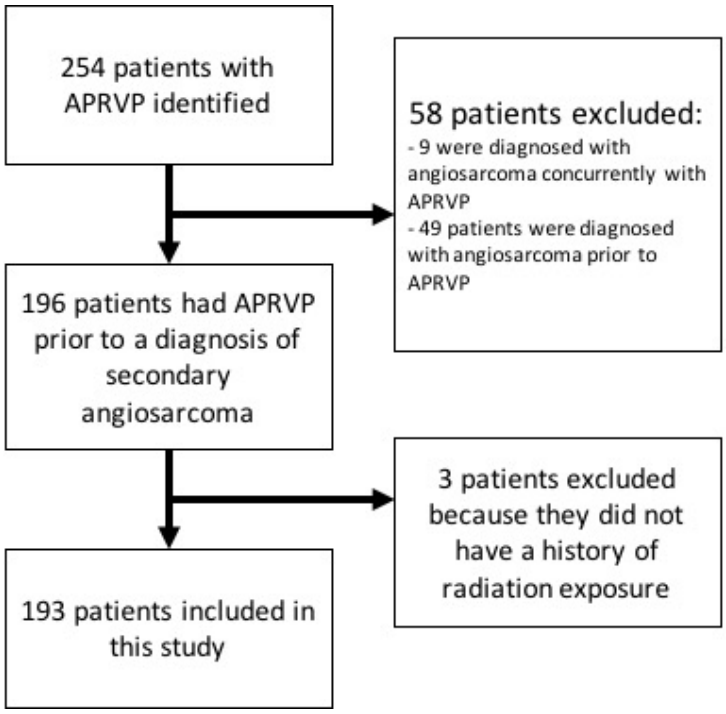


Figure 2: **Varied clinical presentations of APRVP: A) single pink papule, B) diffuse tan-pink macules, C) telangiectatic patch along surgical scar, D) purpuric macules.**

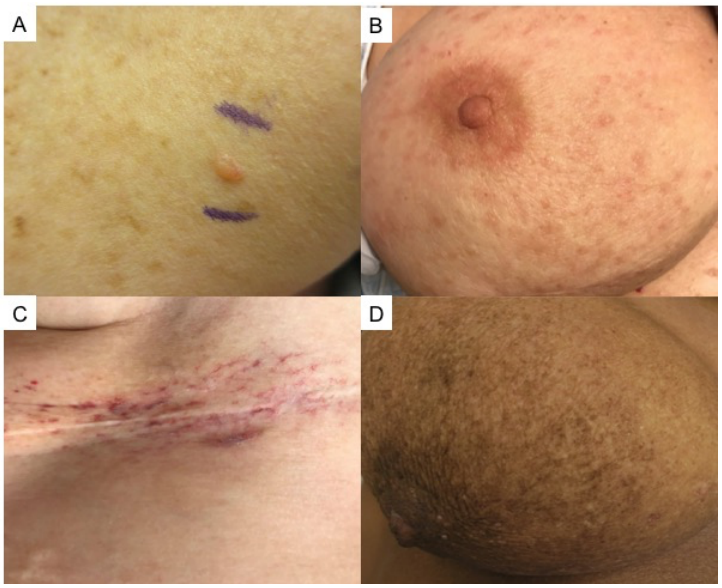


Table 1: **Demographic and clinical features of patients diagnosed with APRVP (n = 193)[1]**

Demographic Features	**Patients with APRVP (n = 193)**
Age of diagnosis of APRVP in years (mean, 95% CI)	61.3 (59.5 – 63.0)
Sex (% female)	190 (98.4%)
Race, n (%) N = 189	
Caucasian Hispanic Asian Black	178 (94.2%) 4 (2.1%) 4 (2.1%) 3 (1.6%)
Smoking status, n (%) N = 82	
Current Former Never	4 (4.9%) 39 (47.6%) 39 (47.6%)
Clinical Features	**Patients with APRVP (n = 193)**
Mutation, n (%) N = 15	
BRCA1 BRCA2 Variant of unknown significance No found mutations	2 (13.3%) 2 (13.3%) 5 (33.3%) 6 (40.0%)
Primary cancers, n (%) N = 163	
Breast Lymphoma Lung Vulvar cancer Anal squamous cell cancer Merkel Cell Carcinoma Melanoma Leiomyosarcoma Synovial sarcoma Angiosarcoma Liposarcoma Desmoid tumor Mucoepidermoid cancer	143 (87.7%) 4 (2.5%) 2 (1.2%) 2 (1.2%) 2 (1.2%) 2 (1.2%) 2 (1.2%) 1 (0.6%) 1 (0.6%) 1 (0.6%) 1 (0.6%) 1 (0.6%) 1 (0.6%)
Radiation characteristics	
Radiation dosage in Gy (median, range) N = 15	50.4, 45 – 64

Time from radiation to disease in years (median, range)[2] N = 127	6, 1-40
Complications of radiation, n (%) N = 100	
Lymphedema Cardiopulmonary restrictive disease Thyroid dysfunction Chronic dermatitis Infection Delayed wound healing Chronic pain from lymphadenopathy	21 (21%) 3 (3%) 1 (1%) 9 (9%) 4 (4%) 3 (3%) 1 (1%)
Treatment, n (%) N = 91	
Excision Monitor	43 (47.3%) 48 (52.7%)
Outcome, n (%) N = 100	
Recurrence Stable or Better Angiosarcoma	20 (20.0%) 77 (77%) 3 (3%)
Time to recurrence in days (median, range)[3]	392, 27-1955
Time from APRVP to angiosarcoma in days (median, range)	229 (54-235)
Deceased, n (%)	10/100 (10%)
Time to death in years (median, range) n = 10	2.3, 0.02-8.2
Follow-up time in years (median, range)	3.2, 0-14.8
Clinical Feature of APRVP lesions	**Patients with APRVP (n = 193)**
Size, n (%) N = 38	
<1 cm 1-2 cm >2 cm	32 (84.2%) 4 (10.5%) 2 (5.3%)
Primary morphology, n (%) N = 96	
Papule Plaque Patch Nodule Macule Vesicle	34 (35.4%) 21 (21.9%) 17 (17.7%) 13 (13.5%) 7 (7.3%) 4 (4.2%)
Secondary features, n (%)	

N = 96	
Induration	13 (13.5%)
Telangiectasia	12 (12.5%)
Edema	6 (6.3%)
Scaling	4 (4.2%)
Pearly/shiny	4 (4.2%)
Bruise-like	2 (2.1%)
Erosion/ulceration	2 (2.1%)
Other features, n (%) N = 96	
On previous scar	8 (8.3%)
Infection (cellulitis, abscess)	2 (2.1%)
Squamous cell carcinoma	1 (1.0%)
Incidental	6 (6.3%)
Number of lesions, n (%) N = 81	
Single	55 (67.9%)
Multiple	26 (32.1%)
Location, n (%) N = 193	
Breast	164 (85.0%)
Axilla	8 (4.1%)
Groin	5 (2.6%)
Back	5 (2.6%)
Abdomen	4 (2.1%)
Head and Neck	2 (1.0%)
Arms	2 (1.0%)
Legs	2 (1.0%)
Buttocks	1 (0.5%)
Symptoms, n (%) N = 96	
Pain	6 (6.3%)
Pruritus	3 (3.1%)
Discharge	5 (5.2%)
Serous	2/5 (40%)
Yellow	1/5 (20%)
Blood	2/5 (40%)

[1] Normality assumption was checked for continuous variables, and mean (95% CI) or median (range), depending on the variable distribution, was reported.

[2] If there are multiple malignancies or cancer recurrences, time from initial radiation treatment to APRVP diagnosis was used.

[3] If there are multiple APRVP recurrences, time to first recurrence was used.

Table 2**:** Comparison of patients with (n = 43) and without excision (n = 48)[1]

	Patients with excision (n = 43)	Patients with monitoring (n = 48)	p-value
Age at APRVP diagnosis (mean, 95% CI)	60.21 (55.80 to 64.62)	59.26 (55.48 to 63.04)	0.611
Date of APRVP diagnosis (mean, 95% CI)	4/18/12 (3/25/04 – 5/24/18)	12/13/14 (8/28/09 – 10/17/18)	0.001*
Follow-up time in days (median, range)	770 (10-5403)	919 (8-3268)	0.915
Race, n (%)			
Caucasian	39/43 (90.7%)	43/48 (89.6%)	0.820
Black	1/43 (2.3%)	2/48 (4.2%)	
Hispanic	1/43 (2.3%)	2/48 (4.2%)	
Asian	0/43 (0%)	0/48 (0%)	
Unreported	2/43 (4.7%)	1/48 (2.1%)	
Age at primary malignancy (mean, 95% CI)	51.44 (45.90 to 56.99)	49.39 (45.95 to 52.83)	0.550
APRVP lesion size in mm (median, range)	6, 3-50 (n = 17)	5, 1-90 (n = 13)	0.736
APRVP primary lesion, n (%)			
Papule	13/27 (48.1%)	10/34 (29.4%)	0.165
Plaque	4/27 (14.8%)	11/34 (32.4%)	
Patch	2/27 (7.4%)	8/34 (23.5%)	
Nodule	5/27 (18.5%)	2/34 (5.9%)	
Macule	2/27 (7.4%)	2/34 (5.9%)	
Vesicles	1/27 (3.7%)	1/34 (2.9%)	
Lesion number, n (%)			
Single	14/22 (63.6%)	24/34 (70.6%)	0.770
Multiple	8/22 (36.3%)	10/34 (29.4%)	
Outcomes of lesions (at last date of follow-up)			
Recurrence	10/43 (23.3%)	4/48 (8.3%)	0.141
Stable or Better	31/43 (74.4%)	43/48 (89.6%)	
Angiosarcoma	1/43 (2.3%)	1/48 (2.1%)	
Recurrence rate[2] per 100 person-years (95% CI)	6.9 (3.3, 12.6)	2.8 (0.8, 7.2)	0.193
Deceased	3/43 (7.0%)	3/48 (6.3%)	1.000

[1] Fisher exact test for categorical variables and Wilcoxon rank sum test for continuous variables were performed. Normality assumption was checked for continuous variables, and mean (95% CI) or median (range), depending on the variable distribution, was reported.

[2] Includes either recurrent APRVP or angiosarcoma

*$p < 0.05$

Figure 3**: Study flow diagram of included patients**

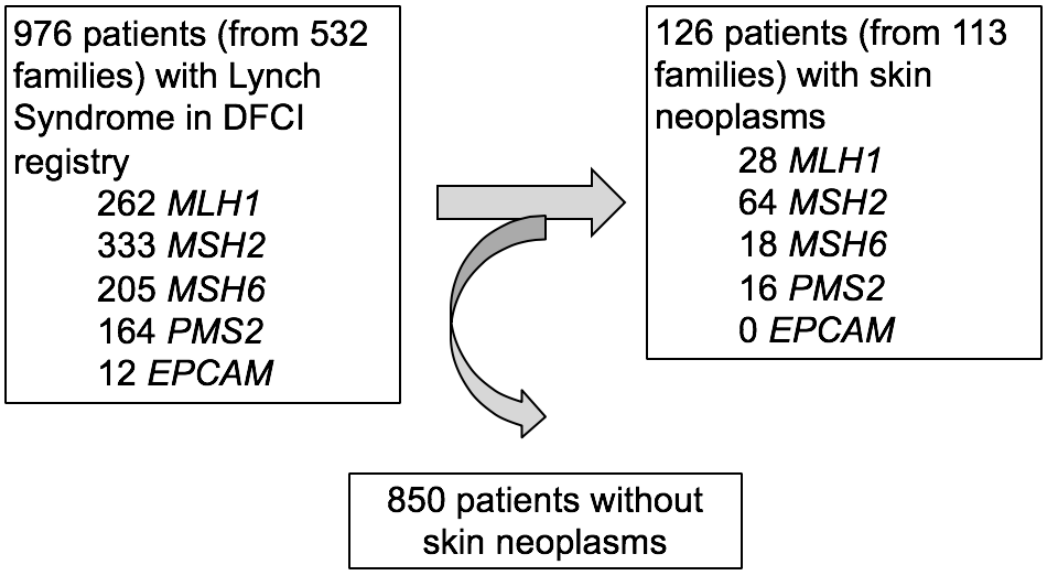
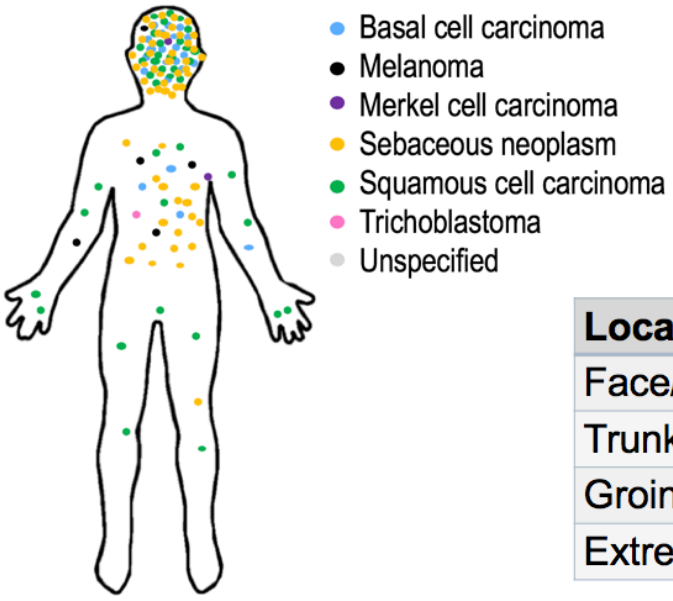


Figure 4**: Location of skin neoplasms (n = 163)**



Location	N (%)
Face/head	109 (67%)
Trunk	29 (18%)
Groin	1 (0.6%)
Extremities	24 (15%)

Table 3**: Demographic and clinical characteristics of Lynch syndrome carriers with skin neoplasms (n = 126)**

Male, n (%)	53/126 (42%)
Race, n (%)	
White	80 (63.5%)
Ashkenazi Jewish	8 (6.3%)
Asian	1 (0.8%)
Mixed	4 (3.2%)
Unknown	33 (26.2%)
Age, median (range)	66.7 (33.5, 98.1)
Skin cancer in Lynch syndrome patients, n (%)	126/976 (12.9%)
MLH1	28/262 (10.7%)
MSH2	64/333 (19.2%)
MSH6	18/205 (8.8%)
PMS2	16/164 (9.8%)
EPCAM	0/12 (0%)
Number of types of cancers,[1] median (range)	2 (0, 7)
Number of patients with cutaneous neoplasm with a history of visceral malignancy	96 (76.2%)
Number of patients diagnosed with cutaneous neoplasm before visceral malignancy[2]	14 (21.2%)
Number of patients with specific skin neoplasm, n (%)[3]	
Basal cell carcinoma	40 (32%)
Melanoma	21 (17%)
Merkel cell carcinoma	2 (2%)
Any sebaceous neoplasm	71 (56%)
Sebaceous adenoma	47 (25%)
Sebaceous carcinoma	20 (16%)
Sebaceous epithelioma	4 (3%)
Any squamous neoplasm	43 (34%)
Squamous cell carcinoma	39 (31%)
Keratoacanthoma	4 (3%)
Trichoblastoma	1 (1%)
Unspecified skin cancer	12 (10%)
Age of initial skin neoplasm,[4] median (range)	
Overall (n = 98)	50 (25, 73)
Basal cell carcinoma (n= 20)	54.0 (29, 70)
Benign sebaceous neoplasm[4] (n = 30)	53.0 (35, 73)
Melanoma (n = 18)	46.5 (33, 65)
Merkel cell carcinoma (n = 1)	72.0 (72, 72)
Sebaceous carcinoma (n = 9)	51.0 (33, 72)
Squamous cell carcinoma[5] (n = 14)	48.5 (25, 71)

Unspecified (n = 6)	48.0 (41, 65)
Age of patients who developed any skin neoplasm,[5] median (range)	
Overall (n = 230)	61 (25, 84)
Basal cell carcinoma (n = 31)	54 (29, 78)
Melanoma (n = 22)	49 (33, 74)
Merkel cell carcinoma (n = 3)	72 (67, 78)
Benign sebaceous neoplasms (n = 91)	73 (35, 79)
Sebaceous carcinoma (n = 23)	54 (33, 77)
Squamous cell carcinoma, including keratoacanthoma (n = 52)	63 (25, 84)
Trichoblastoma (n = 1)	75 (75, 75)
Unspecified skin cancer (n = 7)	46 (41, 65)
Other cancers, n (%)	
Colorectal cancer	60 (47.6%)
Ovarian	12 (9.5%)
Endometrial	32 (25.4%)
Urinary tract	15 (11.9%)
Prostate	12 (9.5%)
Pancreatic ductal adenocarcinoma	2 (1.6%)
Small bowel	7 (5.6%)
Brain	1 (0.8%)
Gastric	4 (3.2%)
Breast	8 (6.3%)
Mesothelioma	1 (0.8%)
Hemangioblastoma	1 (0.8%)
Gallbladder	1 (0.8%)
Pancreatic neuroendocrine tumor	1 (0.8%)
Ampulla of vater cancer	1 (0.8%)
Hepatocellular cancer	1 (0.8%)
Cervical cancer	1 (0.8%)

[1] Cancers as defined as malignant neoplasms. Each different type of skin cancer is counted as a separate cancer.

[2] 66 patients with known age of visceral and cutaneous malignancies

[3] An individual can be included in multiple categories so percentages do not add up to 100

[4] N denotes the number of individuals who had a reported age, not the total number of that type of initial neoplasm.

[5] Accounting for all skin cancers

NMSC in children without risk factors

Table 4**: Patient demographic and clinical characteristics (n = 109).**
Abbreviations: SCC = squamous cell carcinoma, BCC = basal cell carcinoma, Mel = melanoma, NMSC = non-melanoma skin cancer, AK = actinic keratosis

	Without any risk factors	With only iatrogenic risk factors[1]	With only predisposing conditions/ skin lesions[2]	P-value comparing "without any risk factors" group and "iatrogenic risk factors" group	P-value comparing "without any risk factors" group and "predisposing conditions" group
Number of patients	37	21	51	NA	NA
Demographic characteristics					
Gender (% Males)	15 (41)	11 (52)	21 (41)	0.4	1.0
Race [n (%)]				1.0	0.3
White	22/27 (81)	16/19 (84)	29/42 (69)		
Black African American	0 (0)	0 (0)	3/42 (7)		
Hispanic/Latino	4/27 (15)	1/19 (5)	5/42 (12)		
Asian	0 (0)	2/19 (11)	2/42 (5)		
Middle-Eastern	1/27 (4)	0 (0)	2/42 (5)		
American Indian	0 (0)	0 (0)	1/42 (2)		
Other	0 (0)	0 (0)	0 (0)		
Not recorded	10	2	9		
Fitzpatrick skin type [n (%)]				0.3	1.0
I-II	7/12 (58)	7/ 8 (88)	8/14 (57)		
III-IV	5/12 (42)	1/8 (13)	3/14 (21)		
V-VI	0 (0)	0 (0)	3/14 (21)		
Not recorded	25	13	37		
UV index of institution location[3]				1.0	0.1
Low UV index	5 (14)	2 (10)	15 (29)		
Medium UV index	24 (65)	15 (71)	27 (53)		
High UV index	8 (22)	4 (19)	9 (18)		
Age of initial diagnosis in years (median, range)	15 (4.6-19.8)	15 (5.6-19.7)	11 (0.9-19.4)**	0.3	0.002
Clinical characteristics					
Skin cancer type [n (%)]				NA	NA
SCC only	10 (27)	8 (38)	6 (12)		
BCC only	23 (62)	11 (52)	35 (69)		

BCC and SCC only BCC and Mel only SCC and Mel only SCC, BCC, and Mel	1 (3) 2 (5) 1 (3) 0 (0)	0 (0) 2 (10) 0 (0) 0 (0)	6 (12) 2 (4) 1 (2) 1 (2)		
SCC diagnosis [n (%)]	12 (32)	8 (38)	14 (27)	0.8	0.6
BCC diagnosis [n (%)]	26 (70)	13 (62)	44 (86)	0.6	0.1
Melanoma diagnosis [n (%)]	3 (8)	2 (10)	4 (8)	1.0	1.0
Type of lesion [n (%)] SCC in situ SCC invasive Keratoacanthoma BCC Melanoma	 3 (8) 4 (11) 4 (11) 26 (70) 1 (3)	 5 (24) 5 (24) 1 (5) 13 (62) 2 (10)	 6 (12) 14 (27) 2 (4) 44 (86) 4 (8)	 0.1 0.3 0.6 0.6 0.5	 0.7 0.07 0.2 0.1 0.4
Positive family history for NMSC [n (%)]	2/22 (9)	1/15 (7)	5/27 (19)	1.0	0.4
Time from onset of initial SC to dx [months] (median, range)	9 (1.1-72)	4 (0.03-28.1)	12 (1.0-127)	0.2	0.8
Evaluated by dermatology for initial skin cancer [n (%)]	26/30 (87)	19/20 (95)	42/45 (93)	0.6	0.4
Examined by dermatologist prior to developing initial skin cancer [n (%)]	5/14 (36)	6/11 (55)	12/21 (57)	0.4	0.3
Number of skin cancers at initial diagnosis (median, range)	1 (1-3)	1 (1-2)	1 (1-30)**	0.9	0.0003
Total number of skin cancers (median, range)	1 (1-7)	1 (1-6)**	3 (1-126)**	0.002	<0.0001
Type of Precancerous lesion [n (%)] AK Porokeratosis Lentigo Atypical nevi None	 1 (3) 0 (0) 2 (5) 2 (5) 33 (89)	 6 (29)** 1 (5) 2 (10) 4 (19) 10 (48)	 10 (20)* 1 (2) 5 (10) 4 (8) 38 (75)	 0.007 0.4 0.6 0.2	 0.02 1.0 0.7 1.0
Life status [n (%)] Alive Dead Cause of death: Related to SC Unrelated to SC Not recorded	 34 (100) 0 (0)	 21 (100) 0 (0)	 46/48 (96) 2 (4) 1/2 (50) 1/2 (50) 0	NA	0.5
Skin cancer location [n (%)]					

Sun exposed Intermittently sun-exposed Non sun-exposed Not recorded	20 (54) 15 (41) 1 (3) 2	10 (48) 11 (52) 1 (5) 0	38 (78) 27 (53) 2 (4) 1	0.8 0.4 1.0	0.07 0.3 1.0
Patients with subsequent skin cancers [n (%)]	2 (5)	6 (29)*	33 (65)**	0.02	<0.0001

[1] Iatrogenic risk factors were defined as exposure to prolonged immunosuppression (>6 months), radiation therapy, chemotherapy, and voriconazole use.

[2] Predisposing genetic conditions included basal cell nevus syndrome, Basex syndrome, Bloom syndrome, Cockayne syndrome, dyskeratosis congenital, dysplastic nevus syndrome, epidermodysplasia verruciformis, epidermolysis bullosa, Fanconi anemia, Ferguson-Smith, incontinentia pigmenti, Kindler syndrome, Muir-Torre, oculocutaneous albinism, Rombo syndrome, Rothmund-Thomson syndrome, xeroderma pigmentosum, and primary immunodeficiencies. Predisposing skin lesions included burn, chronic ulcer, congenital melanocytic nevus, discoid lupus, epidermolysis bullosa, morphea, nevus sebaceous, and wart.

[3] p-values for UV index were calculated using low vs. medium and high. UV index was based on the mean UV index in North America for the month of August by the National Oceanic and Atmospheric Administration, as defined by Qureshi et al., 2008.

Low UV index group: UV indices 5 or less (Alaska, Maine, Michigan, Minnesota, New Hampshire, Oregon, Pennsylvania, Vermont, Washington, Wisconsin, and Toronto)

Medium UV index: 6 (Connecticut, Delaware, Illinois, Indiana, Iowa, Maryland, Massachusetts, Missouri, Nebraska, New Jersey, New York, North Dakota, Ohio, Rhode Island, South Dakota, and West Virginia)

High UV index: 7 or more (Alabama, Arizona, Arkansas, California, Colorado, Florida, Georgia, Hawaii, Idaho, Kansas, Kentucky, Louisiana, Montana, Mississippi, Nevada, New Mexico, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Utah, Virginia, Washington, DC, and Wyoming)

* $p < 0.05$, when comparing patients without any risk factors with the current column
** $p < 0.01$, when comparing patients without any risk factors with the current column

Figure 5**: Age distribution of patients without identifiable risk factors (n = 37).**

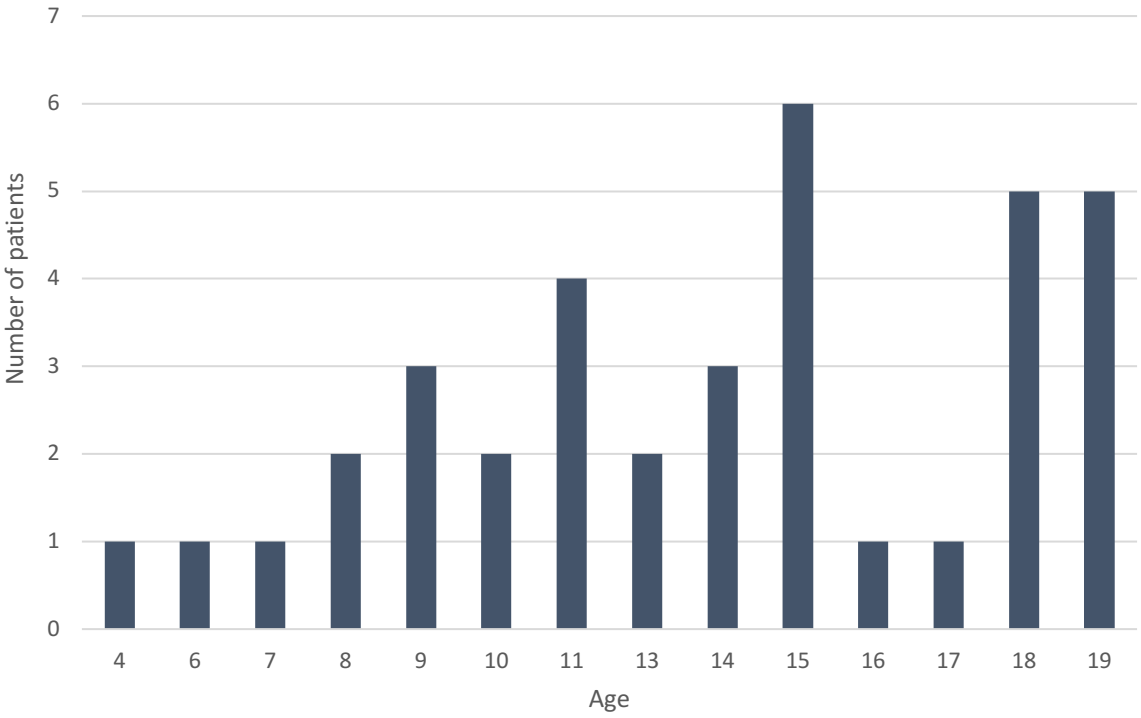
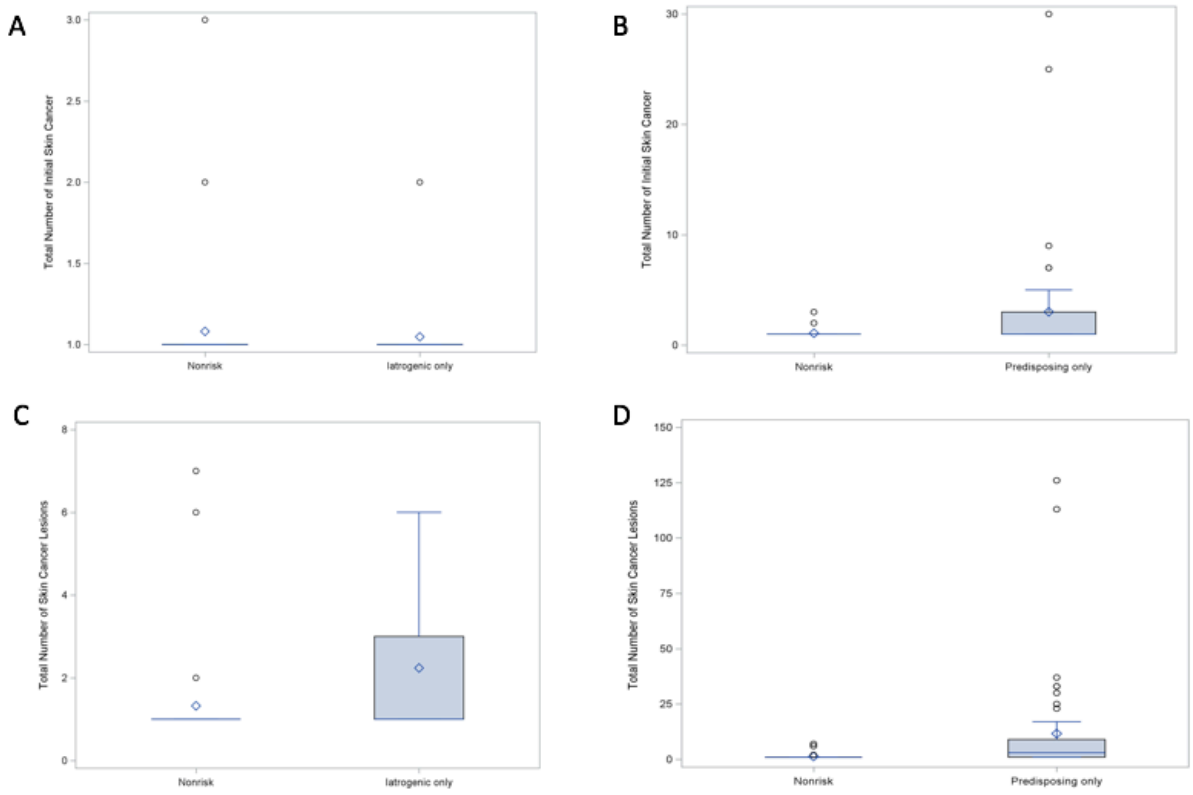


Figure 6: Distribution of number of skin cancers at initial diagnosis in patients without identifiable risk factors (n = 37; median: 1 [range 1-3]) and patients with (A) iatrogenic risk factors (n = 21; median: 1 [range 1-2]; p = 0.9), and (B) predisposing skin conditions (n = 51; median: 1 [range 1-30]; p = 0.0003). Distribution of total number of skin cancers in patients without identifiable risk factors (n = 37; median: 1 [range 1-7]) and patients with (C) iatrogenic risk factors (n = 21; median: 1 [range 1-6], p = 0.002), and (D) predisposing skin conditions (n = 51; median: 3 [range 1-126], p < 0.0001).



Dermatomyositis

Figure 7: Skin findings (A) Centrofacial erythema with involvement of nasolabial fold, (B) photodistributed confluent red purple erythema of upper chest.

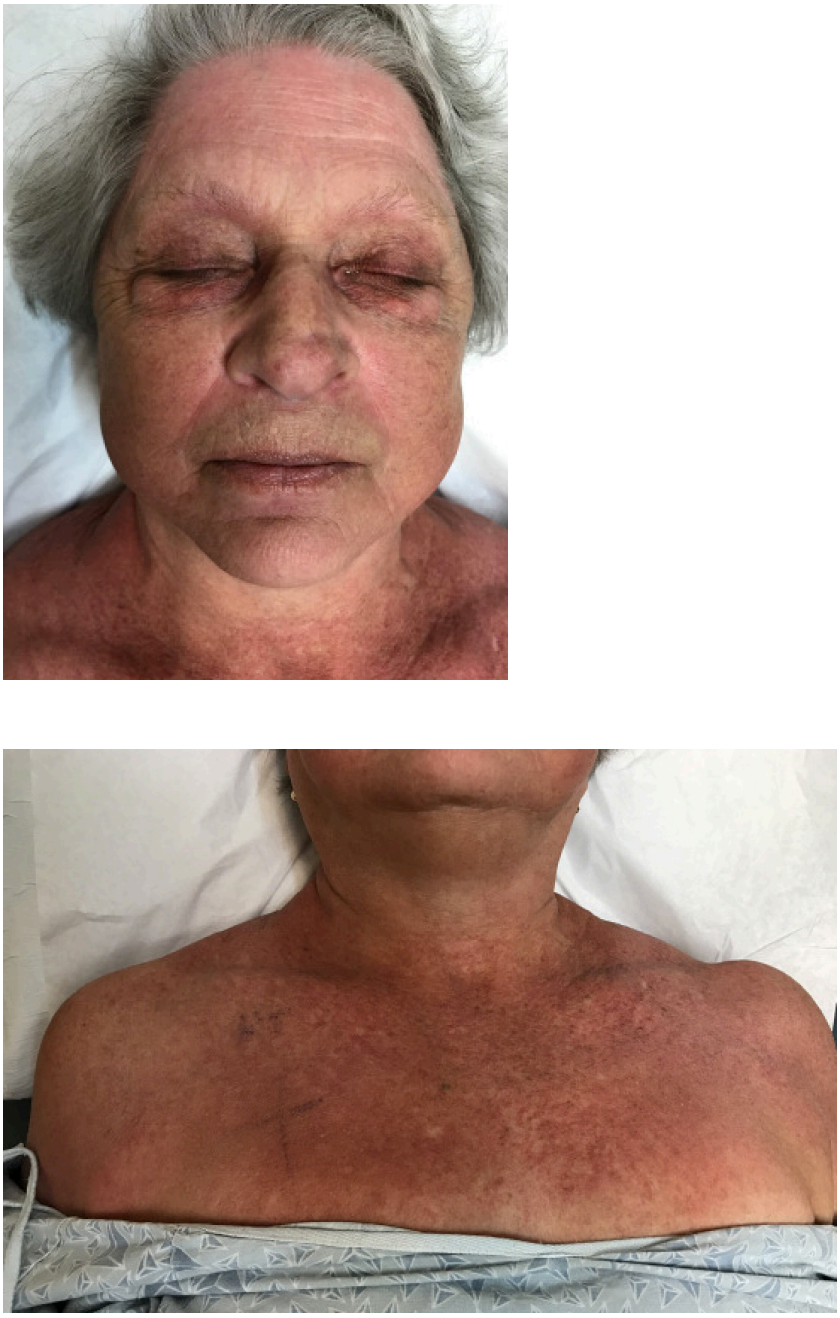
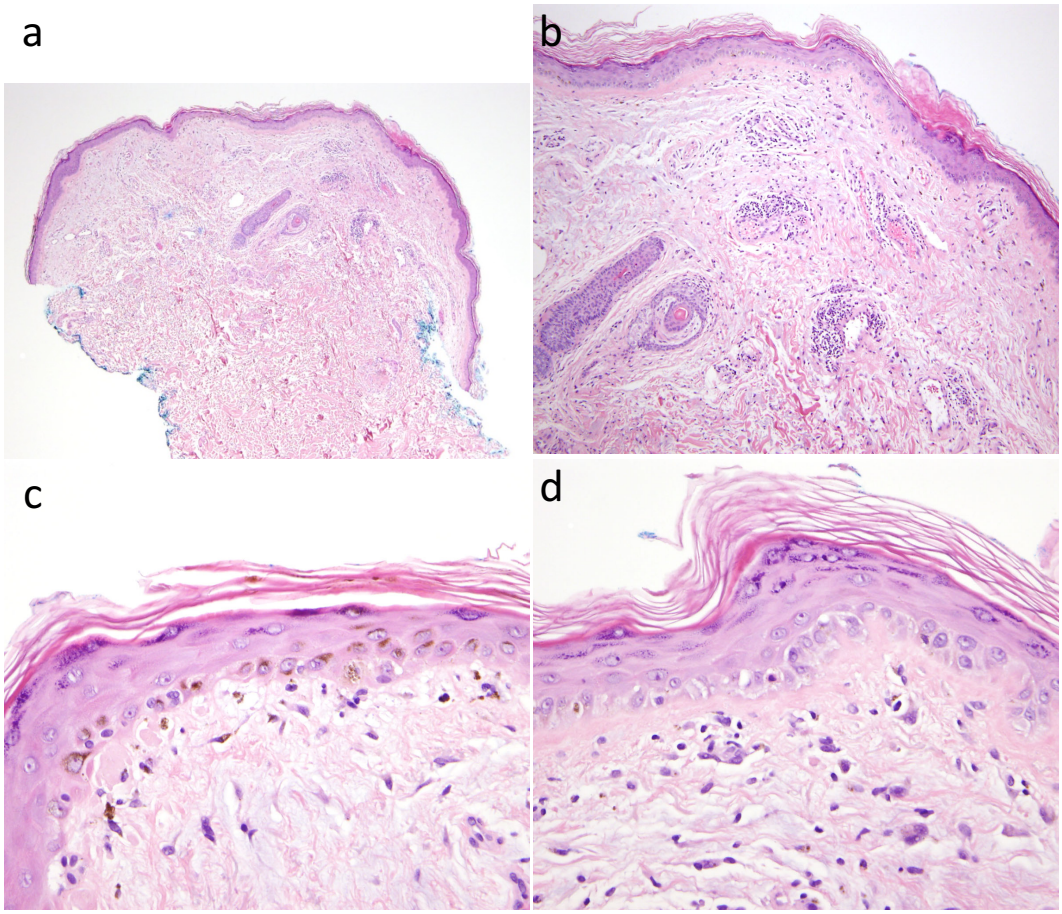


Figure 8: Punch biopsy demonstrating histopathologic features compatible with dermatomyositis (hematoxylin and eosin stain). (A) At low power, a mild superficial dermal perivascular infiltrate and microvascular ectasia can be appreciated. There is epidermal atrophy and focal hyperkeratosis (original magnification x 40). (B) Mild superficial dermal perivascular infiltrate and microvascular ectasia are seen with overlying subtle interface alteration (original magnification x 100). (C) Interface changes are present with basal vacuolar hydropic degeneration and the presence of cytoid bodies. Dermal melanophages are present (original magnification x 400). (D) Interface changes are present with basal vacuolar degeneration, scattered dyskeratotic keratinocytes and a mild superficial dermal inflammatory infiltrate (original magnification x 400).



Erythema multiforme

Figure 9: Target lesions on (A) chest and (B) dorsal hand.

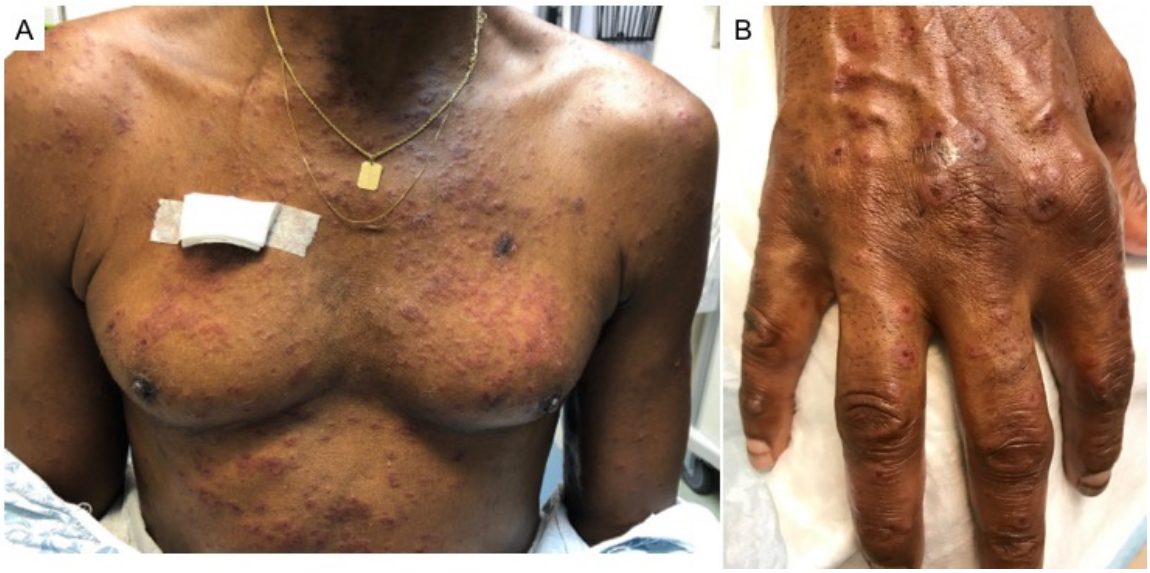


Figure 10: Histopathological image showing vacuolar interface dermatitis with florid dyskeratosis, consistent with erythema multiforme; magnification (A) 10x, (B) 40x.