A Review of Nail Changes in Acrokeratosis Paraneoplastica (Bazex Syndrome)

Bipasha Roy^a Shari R. Lipner^b

^aNew York Medical College School of Medicine, Valhalla, NY, USA; ^bDepartment of Dermatology, Weill Cornell Medicine, New York, NY, USA

Keywords

Acrokeratosis paraneoplastica · Bazex syndrome · Nails · Malignancy · Onychodystrophy · Squamous cell carcinoma

Abstract

Acrokeratosis paraneoplastica (Bazex syndrome) is a rare paraneoplastic dermatosis associated with internal malignancies. Clinical presentation is characterized by erythematous or violaceous scaly plaques involving the digits, nose, ears, palms, and soles. Nail changes commonly present concurrently with cutaneous manifestations. In this review, we characterize nail changes associated with acrokeratosis paraneoplastica. A total of 48 cases were analyzed. Nail findings were nonspecific, with the most common being nail plate thickening, onycholysis, subungual hyperkeratosis, longitudinal ridging, discoloration, and nail plate loss. In most patients, nail changes involved the majority of fingernails and toenails and most often appeared prior to the diagnosis of malignancy. The most common associated underlying malignancies were squamous cell carcinomas of the head and neck. A diagnosis of acrokeratosis paraneoplastica should be considered in patients with onychodystrophy in-

volving multiple nails with accompanying atypical psoriasiform dermatoses. Screening for internal malignancies may significantly decrease morbidity and mortality for these patients.

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Published by S. Karger AG, Basel

Introduction

Bazex' acrokeratosis paraneoplastica is a rare dermatological condition characterized by erythematous and hyperkeratotic plaques, involving the nose, ears, palm, and soles. Bazex syndrome is associated with internal malignancies, commonly of the upper aerodigestive tract [1–3]. Cutaneous manifestations commonly appear prior to cancer diagnosis and typically follow 3 distinct clinical stages. Nail dystrophy often presents during the first stage concurrently with papulosquamous plaques on the distal digits, nose, and ears [1, 4]. Nail findings are common amongst acrokeratosis paraneoplastica patients [1]. Our objectives were to characterize nail changes associated with acrokeratosis paraneoplastica, which may be important clues to the presence of internal malignancies.

Table 1. Demographics, malignancy, treatment, nail changes, and cutaneous manifestations of patients with Bazex syndrome [1, 9–28, 30–38, 40–52]

Author	Age, years	Sex	Skin type	Race	Cancer type	Stage	Metastasis	Treatment	Nails involved	Nail changes	Timing of nail changes in relation to cancer	Cutaneous manifestations
Jacobsen et al. [11]	63	M	Not specified	Not specified	Epidermoid carcinoma of lung	Not specified	Liver metastases	None, patient died of broncho-pneumonia	All finger and toenails	Tender nail folds. Fingernails: hypertrophic, onycholytic, crumbling, and partially destroyed. Toenails: yellow, hypertrophic, onycholysis	6 months prior	Pityriasisform scaling of tip of nose, ear helices, toes and distal fingers. Violaceous keratoderma of fingers, palms, toes, and soles
Richard et al. [12]	55	M	Not specified	White	SCC of esophagus	Not specified	Cervical metastases	Radiotherapy	Majority of fingernails and toenails	Thickened and friable	4 months prior	Erythema with violaceous hue of nose, lips, cheeks, chin, ears, elbows, and knees. Palmo-plantar regions with hyperkeratosis
Bologna et al. [1]	52	M	VI	Black	Metastatic SCC of esophagus	Not specified	R upper lobe nodules and R hilar adenopathy, dermal metastasis SCC	Radiation therapy and cisplatin	All finger and toenails	Thickened, yellow/brown discoloration subungual hyperkeratosis and horizontal and longitudinal ridging	9–10 months prior	Scaling of toes, fingers, and soles. Hyperpigmentation of nose and ears
Douglas et al. [13]	82	M	Not specified	Not specified	Adenocarcinoma of esophagus	Not specified	Mediastinal lymphadenopathy	Palliative radiotherapy	Majority of fingernails and toenails	Longitudinal ridging and distal thickening of nail plates	24 months prior	Bluish erythema and scaling of skin over fingers, toes, thenar, and hypothenar eminences. Keratotic lesions on nose and ears
Handfield-Jones et al. [14]	73	F	II	Caucasian	Poorly differentiated SCC	Not specified	Intrapulmonary metastasis	Radiotherapy	All fingernails and toenails	Ridging splitting clubbing	2 months prior	Purple discoloration of fingers and toes with tissue swelling and psoriasiform scaling
Handfield-Jones et al. [14]	65	M	II	Caucasian	Anaplastic carcinoma of indeterminate origin	Not specified	Cervical lymphadenopathy	Radiotherapy	Toenails only	Loose with sterile paronychia. Subungual and periungual hyperkeratosis	2 months prior	Surrounding skin swollen and purple
Handfield-Jones et al. [14]	73	M	II	Caucasian	SCC of R main bronchus	Not specified	Not specified	Not specified	All finger and toenails	Severe flaking and cracking of nails and warty thickening and fissuring of the nail folds	2 months prior	Dry scaly skin around nails. Thickened and scaling on soles of feet. Purple discoloration of arms and knees. Thickening of skin of axillae
Mounsey et al. [15]	66	M	II	White	SCC of the glottis	T-3, N-0, M-0	No	Total laryngectomy, L anterior neck dissection, L hemithyroidectomy	Majority of fingernails and toenails	Longitudinal ridging and nail plate destruction	Not specified	Palmar and plantar hyperkeratosis and superficial pitting
Poskitt et al. [16]	70	M	III	Not specified	SCC of esophagus	Not specified	Metastasis to tonsil	Excised, digoxin, Navitrex [®] and Oruvail SR	All fingernails and toenails	Longitudinal ridging	5 years post	Erythematous scaling of nose and ears, swollen and cyanotic fingers with scaling, erosion and crusting of cuticles
Arregui et al. [17]	41	M	II	White	SCC of esophagus	Not specified	Lymphadenopathy in the mediastinum and bilateral pulmonary metastases	Palliative treatment with radiotherapy	All fingernails and toenails	Severe onychodystrophy, unspecified	11 months prior	Erythematous eruption in periungual area of fingers and toes. Fine scales at tips of nose and external ears
Arregui et al. [17]	73	M	II	White	Recurrence of transitional cell carcinoma of the bladder	Not specified	Not specified	Treatment of local bladder recurrences with of mitomycin C	All fingernails and toenails	Distal shedding and yellowish discoloration	Few weeks prior	Erythematous, psoriasiform eruption of periungual skin. Moderate plantar hyperkeratosis and desquamative cheilitis
O'Brien et al. [9]	67	F	V	Not specified	Oropharyngeal carcinoma	Not specified	Not specified	5-fluorouracil and carboplatinum	Not specified	Loss of the nail plate	Simultaneously with recurrence	Psoriasiform eruption on fingers and toes extending onto dorsum of hands and feet

Table 1 (continued)

Author	Age, years	Sex	Skin type	Race	Cancer type	Stage	Metastasis	Treatment	Nails involved	Nail changes	Timing of nail changes in relation to cancer	Cutaneous manifestations
Hara et al. [18]	54	M	III	Japanese	Cutaneous SCC of the lower leg	Not specified	Not specified	Cutaneous SCC excision	All fingernails and toenails	Distal onycholysis. Subungual hyperkeratosis and paronychia erythema	3 months prior	Scaling, erythematous plaques on nose, ears, trunk and proximal limbs. Erythematous, thick hyperkeratosis with deep fissures of thenar areas, soles, and palms. Vitiligo and alopecia areata of the scalp
Lacourreye et al. [19]	62	M	Not specified	Not specified	Well-differentiated SCC of pyriform sinus	Not specified	Distant metastasis	Unresectable. Palliative radiotherapy	Not specified	Paronychia and thickening of partly destroyed onycholytic nail	6 months prior	Violaceous psoriasiform erythema and scaling of fingers. Swelling of fingers with periungual acrokeratosis
Wareing et al. [20]	71	M	II	Caucasian	SCC of unknown primary origin	Not specified	Enlarged mediastinal nodes	Radiotherapy	All finger and toenails	Ridges and ragged cuticles	18 months prior	Psoriasiform scaling of fingers, lower shins and buttocks. Hyperpigmentation over bridge of the nose
Sarkar et al. [21]	61	M	III	White	SCC of the L pyriform sinus	T-3, N-0, M-0	No	Total laryngectomy, partial pharyngectomy and left radical neck dissection	All fingernails and toenails	Yellowish discoloration and periungual swelling	5 years prior	Acral hyperkeratotic skin lesions and squamous skin lesions at elbows, hands and feet. Painful fissures and scales on heels
Mutasim et al. [22]	67	M	VI	Black	Moderately differentiated SCC of larynx and vocal cords	Not specified	Not specified	Total laryngectomy, R radical neck dissection, and L modified radical neck dissection	Majority of fingernails and toenails	Loss of the cuticles, swelling of the nail folds, subungual hyperkeratosis, transverse and longitudinal ridging with nail loss	Few weeks prior	Hemorrhagic vesicles of dorsal fingers, hands, feet, ankles, and knees. Erythematous/scaly/fissured papules and plaques on palmar hands fingers, toes. Dusky erythema of the nose and ears
Hsu et al. [23]	63	M	IV	Not specified	Adenocarcinoma of colon	Stage B1	No	Low anterior resection	All toenails only	Dystrophic toenails and subungual hyperkeratosis	1 month prior	Pruritic lesions and vesicles on both feet. Dense scale of palms and soles, with fissures on feet. Similar skin lesions on both ears
Buxtorf et al. [24]	58	M	Not specified	Not specified	Low-differentiated SCC of the tongue	T-2, N-1, M-0	No	Chemotherapy and radiotherapy	All fingernails and toenails	Subungual hyperkeratosis and onycholysis	4 months prior	Scaly erythematous, violaceous plaques on ears and tip of nose with hyperkeratosis of toes and fingers
Gill et al. [25]	59	M	Not specified	Not specified	SCC of R Pyriform fossa	Not specified	Not specified	Not specified	Majority of fingernails and toenails	Nail dystrophy, thickened, and friable	4 months prior	Tense bullae on lateral feet with erythematous hyperkeratotic skin. Violaceous plaques of dorsum nose, outer helices and R lateral lower leg
Chave et al. [26]	65	M	V	Indian	Well-differentiated thymic carcinoma	Stage III	Lung parenchyma and pleural metastases	Surgically debulked and radiation therapy	All toenails	Thickened and dystrophic	2 months prior	Violaceous hyperkeratotic plaques on trunk and limbs
Rao et al. [27]	62	M	V	Indian	Adenocarcinoma of rectosigmoid junction	Not specified	Not specified	Not specified	A few nails of the hands and feet	Thickening and brownish discoloration of nail plates with subungual hyperkeratosis	24 months prior	Hyperpigmented scaly papules and plaques over dorsum and palmo-plantar surfaces of hands and feet
Valdivielso et al. [28]	64	M	III	Not specified	SCC of the lung	Stage IIIA (T-2, N-2, M-0)	No	Chemotherapy with carboplatin and paclitaxel	All fingernails and toenails	Longitudinal streaks, subungual hyperkeratosis, and onychomadesis	2 months prior	Symmetrical red violaceous plaques on dorsum of fingers, hands and feet. Thickening of phalanges and hyperkeratotic plaques on palms and soles. Hyperpigmented plaques and scaly on nasal dorsum and both ears

Table 1 (continued)

Author	Age, years	Sex	Skin type	Race	Cancer type	Stage	Metastasis	Treatment	Nails involved	Nail changes	Timing of nail changes in relation to cancer	Cutaneous manifestations
Viteri et al. [29]	51	M	II	Not specified	Metastatic SCC of esophagus	Not specified	Metastatic	Early death of pt	Not specified	Nail detachment with subungual hyperkeratosis	Simultaneously	Hyperkeratotic symmetrical lesions on palms, soles, groin, and scalp
Karabulut et al. [30]	57	F	Not specified	Not specified	Adenocarcinoma of the choledoch	Not specified	Not specified	Refused further medical/surgical therapy	Not specified	Subungual hyperkeratosis and longitudinal ridging	2 months prior	Dusky red psoriasiform plaques, with fine scales on scalp, eyebrows, nasal radix, cheeks, aural helices and gluteal areas; moderate hyperkeratosis on palms and soles
Sator et al. [31]	71	M	II	Not specified	Liposarcoma in the R retroperitoneum	Not specified	Not specified	Two tumor extirpations and radiation therapy	All fingernails	Yellowish discoloration and were slightly thickened	4 months post	Erythematous/amoebic plaques on knuckles, fingernails, fingertips, palms, ears, elbows, and neck and diffuse reddening with telangiectasias in face and upper chest
Strobel et al. [32]	58	M	Not specified	Not specified	SCC of L upper lobe of lung	Not specified	Cervical lymph node metastasis	Radical neck dissection and radiotherapy. Partial lung resection and radical hilar and mediastinal lymphadenectomy	Not specified	Subungual hyperkeratosis with onycholysis	Not specified	Psoriasiform dermatitis of the nose, helix of the ears, fingers and toes
Poligone et al. [33]	62	M	VI	Black	SCC of the esophagus	Stage III	No lymphadenopathy	Localized radiation therapy with adjuvant 5-fluorouracil and cisplatin	Not specified	Thickening with ridging	2 months prior	Hyperpigmented, erythematous plaques with scales on ears and dorsal surfaces of metacarpophalangeal, proximal interphalangeal, and distal interphalangeal joints of hands and feet.
Taher et al. [10]	68	F	II	Caucasian	Invasive lobular carcinoma of the L breast	Not specified	Metastatic infiltration of the lungs, bones (cervical spine, femur, pelvis), and mediastinal lymph nodes	Mastectomy and radiation. Docetaxel epoetin alpha	Majority of fingernails and toenails	Fissuring, onycholysis, and nail dystrophy	Simultaneously with recurrence	Hyperkeratotic plaques and ulceration on dorsum of hands. Fissured, scaly plaques and papules on periorbital skin, nose, forehead, chin, and ears
Bae et al. [34]	63	F	III	Korean	Adenocarcinoma of colon	T-3, N-1, M-0	No	L hemicolectomy	Majority of fingernails and toenails	Onycholysis	1 month prior	Yellowish punctuate hyperkeratotic lesions on palms and soles
Medinica et al. [35]	50	M	IV	White	SCC of the esophagus	Not specified	No	Esophageal resection, subtotal esophagectomy	All fingernails	Yellowish, dystrophic, with subungual hyperkeratosis	3 months prior	Violaceous erythema, edema, and yellow crusts on nose, chin and auricles. Erythematous plaques on elbows and knees. Palmar and plantar regions with diffuse yellow hyperkeratosis and fissures
Cucitti et al. [36]	55	M	I	White	Adenocarcinoma of lung	T-2, N-0, M-0	No	Upper R lobectomy	All fingernails and toenails	Yellowish discoloration with onychodystrophy	3.5 years prior	Erythematous hyperkeratotic lesions of the peritungal region
Ljubenovic et al. [37]	56	M	Not specified	Not specified	Anaplastic metastatic carcinoma, unspecified. Pt died before primary tumor found	Not specified	Yes	Patient died	Some finger and toenails	Moderate dystrophic changes, unspecified	1 month prior	Hyperkeratotic skin changes on his palms, fingers, soles, tip of nose and on earlobes

Table 1 (continued)

Author	Age, years	Sex	Skin type	Race	Cancer type	Stage	Metastasis	Treatment	Nails involved	Nail changes	Timing of nail changes in relation to cancer	Cutaneous manifestations
Santos-Silva et al. [38]	61	M	II	Caucasian	SCC on lateral border of the tongue	T-2, N-0, M-0	No	L Hemiglossectomy and supraomohyoid neck dissection. Post-operative radiotherapy	All fingernails and toenails	Vertical ridging widespread thickening, onycholysis	2 months post	Ulcerations involving lips, buccal mucosa and tongue. Scales on dorsal surfaces of metacarpophalangeal and interphalangeal joints of hand. Mucosa of the glans penis exhibit diffuse red patches
Goto et al. [39]	75	M	IV	Japanese	Hepatocellular carcinoma (HCC)	Not specified	Not specified	Partial resection of segment VIII of the liver	All fingernails and toenails	Dystrophic, unspecified	1 month prior	Thick hyperkeratosis of palms and soles, and scaly erythematous lesions on face and earlobes. Solid reddish papules on the trunk
Zarzour et al. [40]	58	F	VI	African American	Small cell lung carcinoma	Not specified	Lesion in the liver consistent with metastatic disease	Palliative chemotherapy	Majority of fingernails and toenails	Brittle and atrophied	24 months prior	Hyperkeratotic plaques on hands and joints. Hyperpigmented macules over dorsal arms and lower legs. Hyperpigmented, scaly patch on nose
Rodrigues junior et al. [41]	73	F	V	Not specified	SCC of the esophagus	Not specified	Hepatic nodules and lymphadenopathy	None, patient died	All fingernails and toenails	Yellow hyperchromia and onychomadesis	2.5 months prior	Violet, desquamative lesions on nose, auricular pavilions, dorsal hands, feet, and toes. Symmetric palmoplantar keratoderma, with lamellar desquamation
Fleming et al. [42]	70	F	I	Not specified	Metastatic undifferentiated (SCC), primary lesion not identified	Not specified	Liver metastases and cervical lymphadenopathy	Modified neck dissection and radiotherapy	9 fingernails and 1 toenail – spread to all nails	Initial presentation - candidal onychomycosis; 4 months later: subungual debris, and loss of cuticles in all nails	24 months prior	Painful, swollen, and erythematous, with scale on dorsal surface. Fine scale in the corneal bowls, antihelix and left ear lobe
Graves et al. [43]	60	M	VI	Not specified	Basaloid SCC of supraglottic region	Not specified	Diffuse metastases to the bones and viscera	Palliative radiotherapy	All fingernails	Onychomadesis, nail tenderness	3 weeks prior	Hyperkeratotic, erythematous and hyperpigmented papules/plaques on chest, back, bilateral palms and arms. Erythematous plaques on the glans penis
Robert et al. [44]	73	F	IV	Not specified	Gastric adenocarcinoma	Not specified	Ovarian metastases	FOLFOX4 chemotherapy	Mainly L fingernails, and R fingernails and toenails	Nail lesions, unspecified	2 months prior	Skin lesions, unspecified
Amano et al. [45]	82	M	III	Japanese	R lung (SCC), hx of tongue, and gastric cancer	Not specified	Not specified	Lung lobectomy	All finger and toenails	Nails were thickened and fissures	6 months prior	Hyperkeratotic erythematous plaques on bilateral palms and soles
Squires et al. [46]	56	F	VI	Not specified	Cervical SCC	FIGO stage IIB	Not specified	Pelvic external beam radiotherapy, brachytherapy, and chemotherapy	R Fifth fingernail	Irregular pitting	2 months prior	Scaly hyperpigmented plaques on bilat hands and periungual skin of fingers, with fissuring. Bilat plantar feet demonstrated hyperkeratosis. Xerotic scaling and excoriations on bilateral upper arms, lower legs, and lower back
Vatandoust et al. [47]	69	M	II	Not specified	Metastatic cutaneous SCC of L forearm	Not specified	L axillary area	Excision, cisplatin and 5-fluorouracil	Not specified	Nail changes present not specified	18 months prior	Hyperkeratosis and desquamation
Zhao et al. [48]	83	M	III	Not specified	Pulmonary adenocarcinoma of R lower lobe with local metastatic nodules	Not specified	Diffuse bone metastases. Mediastinal swollen lymph nodes	Gefitinib tablet 250 mg	All fingernails	Yellow-brown and thickened, with subungual keratotic debris	60 months prior	Infiltrative erythematous plaques with scales on nose, cheeks, ears, and dorsa of interphalangeal joints. Erythema covered with yellow thick crust on knees

Table 1 (continued)

Author	Age, years	Sex	Skin type	Race	Cancer type	Stage	Metastasis	Treatment	Nails involved	Nail changes	Timing of nail changes in relation to cancer	Cutaneous manifestations
Shikino et al. [49]	84	M	III	Not specified	Poorly differentiated laryngeal SCC	T-4a, N-2c, M-0	No	Radiation therapy	All fingernails	Yellow discoloration and proximal detachment	2 months prior	Symmetric hyperkeratotic plaques of distal hands and feet. Violaceous desquamation on ears and nose
Adelman et al. [50]	56	F	II	Not specified	Poorly differentiated laryngeal SCC	T-2, N-2c, M-0	No	Chemoradiation with cisplatin	All finger and toenails	Ridging of nail beds and lifting of nails	2 months post	Scaling over all fingers and toes. Dry gangrene on distal right third digit
Dabas et al. [51]	50	M	V	Not specified	Poorly differentiated SCC of base of the tongue	T-2, N-2c, M-1	Centrilobular nodules in both lungs, consolidation in R upper and lower lobes, enlarged mediastinal lymph nodes	None, patient died	All finger and toenails	Subungual hyperkeratosis, yellowish discoloration and thickening	5 weeks prior	Symmetrical lichenoid scaly plaques on ears, and dorsum of hands
Mititelu et al. [52]	72	F	III	Not specified	NSCLC	Not specified	Not specified	Resection of the R upper lung lobe. Declined adjuvant chemotherapy	All finger and toenails	Thickened with longitudinal ridging and yellow discoloration	4 months prior	Hyperkeratotic and fissured erythematous plaques on bilateral palmoplantar surfaces and lateral digits. Mild scaling on knees

NSCLC, non-small-cell lung carcinoma; SCC, squamous cell carcinoma.

Table 2. Summary of primary cancer locations and types of in patients with Bazex syndrome

Primary cancer: location and type	Cases	Percentage
Carcinoma of head and neck region	21	44
SCC of the esophagus	8	38
SCC of the larynx and vocal cords	4	19
SCC of the tongue	3	14
SCC of pyriform sinus	3	14
Oropharyngeal carcinoma	2	10
Adenocarcinoma of the esophagus	1	5
Carcinoma of the lung	10	21
SCC	6	60
Epidermoid carcinoma	1	10
Adenocarcinoma	1	10
Small-cell lung carcinoma	1	10
NSCLC	1	10
Gastrointestinal carcinoma	6	12
Adenocarcinoma of Colon	2	32
Gastric adenocarcinoma	1	17
Adenocarcinoma of colon	1	17
Adenocarcinoma of the choledoch	1	17
Adenocarcinoma of rectosigmoid junction	1	17
Hepatocellular carcinoma		
Genitourinary carcinoma	2	4
Cervical SCC	1	50
Transitional-cell carcinoma of bladder	1	50
Cutaneous carcinoma	2	4
SCC	2	100
Carcinoma of breast	1	2
Lobular carcinoma	1	100
Sarcoma	1	2
Liposarcoma of retroperitoneum	1	100
Thymic carcinoma	1	2
Indeterminate origin	4	8
SCC	2	50
Anaplastic carcinoma	2	50

SCC, squamous cell carcinoma; NSCLC, non-small-cell lung carcinoma.

Methods

The PubMed database was reviewed for the keywords “Bazex Syndrome and nail,” “Acrokeratosis paraneoplastica and nail,” “Acrokeratosis paraneoplastica,” and “Bazex Syndrome.” The search was limited to articles in the English language published between January 1, 1972, and July 15, 2020. In the initial search, 103 articles were identified and 36 were excluded because they did not pertain to acrokeratosis paraneoplastica, leaving 67. Of the 67 remaining articles, 19 did not report any nail changes, leaving a total of 48 articles for final analysis. Cases were analyzed for age, gender, Fitzpatrick skin type, race, primary cancer type, cancer staging, presence of metastasis, cancer treatment, nails involved, nail clinical presentation, and cutaneous findings. Fitzpatrick skin type was determined by examining photos in the articles and using

Table 3. Summary of nail findings in patients with Bazex syndrome

Nail changes	Percentage
Thickening/onychauxis	35
Subungual hyperkeratosis	31
Yellow/brown discoloration	27
Onycholysis	27
Longitudinal ridging	25
Loss/destruction of nail plate	13
Fissuring	8
Onychomadesis	6
Paronychia	6
Horizontal ridging	4
Tenderness of nail	4
Crumbling/cracking	4
Loss of cuticles	4
Irregular pitting	2
Brittle	2
Atrophy	2
Candidal onychomycosis	2
Clubbing	2
Unspecified	13

the Fitzpatrick classification guidelines [5]. If photos or descriptions of the patient's skin type were unavailable or photos were black and white, they were recorded as not specified.

Results

There were 48 cases of acrokeratosis paraneoplastica with nail changes included in the final analysis. Demographics and case findings are shown in Table 1. Of these patients, 25% were female, with a mean age of 62.5 years (range 41–84 years). Fifteen patients (31%) were classified as Fitzpatrick skin type I–II, 13 patients (27%) as type III–IV, eleven (23%) patients as type V–VI, and 9 patients (19%) not specified. Eleven patients (23%) were described as either Caucasian or White, 4 patients (8%) African American or Black, 7 patients (14%) Japanese, Korean, or Indian, and the races of 26 patients (55%) were not specified.

Primary malignancies were most often localized to the head and neck region (42%) and were most commonly squamous cell carcinomas (SCCs) of the esophagus. SCCs of the larynx, tongue, and oropharynx were also common forms of malignancies within the head and neck region. The lung was the second most common site of malignancy (21%), with mostly SCCs (6 patients). Gastrointestinal carcinomas represented 12% of the cases, most commonly adenocarcinomas. Genitourinary, cutaneous, breast,

Fig. 1. Acrokeratosis paraneoplastica. Nail plate yellowing, onycholysis, and subungual hyperkeratosis in a 51-year-old male with metastatic SCC of the esophagus. This figure has been reproduced with permission of Elsevier (Viteri et al. [29]). SCC, squamous cell carcinoma.

Fig. 2. Acrokeratosis paraneoplastica. Nail plate thickening and yellow and brown discoloration of all fingernails and toenails in a 75-year-old male with hepatocellular carcinoma. This figure has been reproduced with permission of John Wiley and Sons (Goto et al. [39]).

and thymic carcinomas were also reported as primary malignancies. Approximately 8% of the cases involved carcinomas were of indeterminate origin (Table 2). Metastases were present in 22 cases (46%), not present in 12 cases (25%), and not specified in 14 (29%) cases.

Nail changes in acrokeratosis paraneoplastica patients were nonspecific and varied (Table 3). The most common nail findings were nail plate thickening (35%), subungual hyperkeratosis (31%), yellow/brown nail plate discoloration (27%), onycholysis (27%), longitudinal ridging

(25%), and loss or destruction of the nail plate (13%) (Fig. 1, 2). Paronychia was seen in 6% of the cases, often causing pain. Many patients had 2 or more nail findings concurrently; nail plate thickening and subungual hyperkeratosis were most common. Approximately, 79% of the patients had nail findings prior to cancer diagnosis, with onychodystrophies on average presenting in the preceding 10 months. In about 10% of the patients, nail changes occurred following malignancy diagnosis with an average of 14 months post-diagnosis. Nail findings presented concurrently with the diagnosis of cancer in about 6% of the cases, and the timing of nail findings were not specified in 5% of the cases. The majority of fingernails and toenails were involved in all cases except for one in which the onychodystrophy was limited to one fingernail.

Discussion

In our review of 48 cases of acrokeratosis paraneoplastica with nail findings, 36 patients (75%) were males, with a mean age of 62.5 years, and the majority of patients were either Caucasian or White (23%). The majority of patients were of Fitzpatrick skin type I–II (31%), followed by skin type III–IV (27%), and skin type V–VI (23%). Our findings are consistent with those of Bolognia et al. [1], who reviewed 93 cases of acrokeratosis paraneoplastica (with and without nail findings) and reported that 89/93 patients were males (96%) with a mean age of 60 ± 8.5 years. In a more recent review on Bazex syndrome (not nail specific) by Räßler et al. [6], 54/70 (77%) patients were males, with mean ages of 65 and 62 years for patients with nail findings and no nail findings, respectively.

In our study of Bazex patients with nail findings, malignancies were most commonly localized to the head and neck (44%), followed by the lung (21%), and gastrointestinal tract (12%). In addition, metastatic anaplastic tumors and SCCs of unknown primary origins accounted for 8% of the cases. Other types of carcinomas in our review included cervical SCC, transitional-cell carcinoma of the bladder, lobular carcinoma of the breast, liposarcoma, cutaneous SCCs, and thymic carcinoma. SCCs of the head and neck were also the most commonly reported underlying malignancies in Bazex syndrome, in patients with and without nail findings, in prior reviews. Bolognia et al. [1] reported that 57/93 patients (61%) had SCC of the esophagus, larynx, or pharynx. Other common sites included the lung and the gastrointestinal tract. Räßler et al. [6] reported that 11/77 patients (14%) had a primary malignancy of the lung, 8/77 patients (11%) had adeno-

carcinoma of the gastrointestinal tract, and 6/77 cases (8%) had metastatic anaplastic tumors of unknown origins with lymph node metastases of occult carcinomas. There was a case of T-cell lymphoma [7] and a neuroendocrine tumor [8] in patients with acrokeratosis paraneoplastica; however, those patients did not present with any nail changes.

We found that nail changes presented at an average of 10 months prior to malignancy diagnosis for 79% of the Bazex patients. In 2 cases, nail changes presented simultaneously with carcinoma recurrence [9, 10]. Our nail data are consistent with those of Bolognia et al. [1], who reported that in 63% of the Bazex patients, cutaneous manifestations preceded the diagnosis of malignancy, at an average time of 11 months. Nail findings typically appeared concurrently with the initial cutaneous manifestations; Bazex and Griffiths [4] described the cutaneous presentation of acrokeratosis paraneoplastica occurring in 3 stages. In the first stage, papulosquamous plaques present on the distal digits, nose, and ears, along with nail dystrophy [1, 4]. In the second stage, the papulosquamous plaques extend to the cheeks, palms, and soles. In the third stage, typically when metastases occur, the plaques spread to the elbows, knees, and dorsae of the hands and feet [1].

In our review, the most common nail changes were nail plate thickening, subungual hyperkeratosis, yellow or brown nail plate discoloration, onycholysis, longitudinal ridging, and loss or destruction of nail plate. Presentation with 2 or more nail changes simultaneously was frequent. Paronychia, while less common than some of the other nail findings, is an important source of morbidity in these patients. Bolognia et al. [1] reported on similar nail findings associated with acrokeratosis paraneoplastica as in our study; less common nail changes were macerated nails, atrophy, slow growth, and nail plate loss.

Our review is subject to several limitations. Due to the rarity of Bazex Syndrome, there were only 48 cases with associated nail findings published. In some case reports, photograph quality was insufficient to characterize specific nail changes, and/or detailed descriptions of nail findings and digits affected were lacking. Patient demographics were not reported in some cases, and Fitzpatrick skin types were not discernible for others.

A broad variety of nail findings are associated with acrokeratosis paraneoplastica, with many patients presenting with more than one type of onychodystrophy. The changes often affected most or all nails and presented concurrently with cutaneous findings. No nail changes were diagnostic or specific. The presence of subungual

hyperkeratosis, onycholysis, nail plate thickening, longitudinal ridging, onychomadesis, yellow or brown nail plate discoloration, paronychia, nail plate loss and less common changes such as horizontal ridging, onychomycosis, atrophy, clubbing, pitting, and fissuring involving most or all nails should raise suspicion for acrokeratosis paraneoplastica, especially accompanied by the characteristic cutaneous lesions. When a patient presents with papulosquamous plaques on the skin accompanied by nail dystrophy, psoriasis is an important diagnostic consideration. Nail clippings and/or cultures may be performed to rule out other nail conditions in the differential diagnosis, such as onychomycosis or nail psoriasis. In the absence of hyphae, infiltration of neutrophils, and subungual hyperkeratosis in nail plate clippings, dermatologists should be prompted to perform a thorough review of systems, physical examination with palpation of lymph nodes, and referral to primary care for age appropriate malignancy screening and further testing if dictated by physical findings. Since nail changes typically present almost a year prior to diagnosis of malignancy, careful examination of the nails, hands, and digits and appropriate malignancy workup may be lifesaving. In addition, nail alterations in patients with acrokeratosis paraneoplastica should be monitored closely, since onychodystrophies may present during disease recurrence.

Conflict of Interest Statement

The authors have no conflict of interest to declare. This manuscript was not funded. This work has not been previously presented and is not under consideration at any other journal. No reprints requested.

Funding Sources

The authors did not receive any funding.

Author Contributions

Ms. Bipasha Roy has contributed to the conception and design of the work, acquisition, analysis, and interpretation of the data. Bipasha Roy has contributed to drafting the work and revising it critically, has been involved in the final approval of the version to be published, and agrees to be accountable for all aspects of the work in ensuring that questions related to accuracy or integrity of any part of the work are appropriately investigated and resolved.

Dr. Shari Lipner has contributed to the conception and design of the work, acquisition, analysis, and interpretation of the data. Dr. Shari Lipner has contributed to drafting the work and revising it critically, has been involved in the final approval of the version to be published, and agrees to be accountable for all aspects of the work in ensuring that questions related to accuracy or integrity of any part of the work are appropriately investigated and resolved.

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