

# Paraneoplastic syndromes in patients with keratinocyte skin cancer

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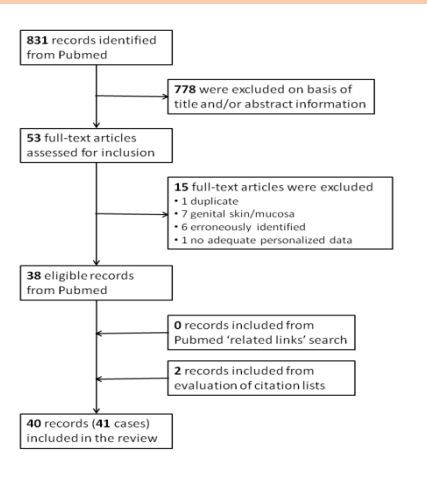
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## BACKGROUND

Paraneoplastic syndromes (PNS) are frequent, non-metastatic tumor-associated findings caused by malignancies in remote body sites. Most PNS are attributed to either endocrine phenomena or to autoimmunity mediated immunological mechanisms. Although the skin is a frequent target of PNS of tumors arising in extracutaneous sites, PNS have been rather rarely reported during skin neoplasms. Herein, we compile published evidence of PNS associated with the growth of keratinocyte skin cancers (KSC).

## MATERIALS AND METHODS

Only paraneoplastic syndromes attributed to KSC, i.e. cutaneous squamous cell carcinomas (cSCC), basal cell carcinomas (BCC) and skin adnexal neoplasms were included. MEDLINE was searched using Pubmed for publications reporting PNS attributed to KSC, ((C)) with following search strategy: {C} = {A} AND {B}, with {A} = {{{basal cell carcinoma} OR (BCC)} OR [{{squamous cell carcinoma} OR (sc)}] AND [{{cutaneous} OR (skin)}}] OR [keratinocyt\* skin cancer] OR [{{skin cancer} NOT (melano\*)}] and {B} = {paraneopl\*} OR (BN), with (BN) = {B1} OR {B2} OR... OR {Bi} OR ... OR {B43}. Bi= {text i} represents a paraneoplastic syndrome in text form, with Bi the <sup>i</sup>th of the 43 PNS (i=1-43), listed in the review article by Bilynsky et al [1]. Starting with the initially returned 831 papers we finally localized 40 papers reporting 41 PNS cases associated with KSC (Figure 1).



**Figure 1.** Literature search: Flowchart of selection process

## CONCLUSIONS

- Most KSC-related PNS were associated with advanced cSCC.
- Malignancy associated hypercalcemia was the most frequently reported PNS in KSC.
- Descriptions of paraneoplastic syndromes in KSC are scarce, probably reflecting a limited capacity of KSC to provoke pathophysiologic mechanisms leading to overt PNS.

## PERSPECTIVE

With the wider application of the emerging treatment modalities, particularly immunotherapy, for advanced KSC the need to differentiate between adverse events and PNS may probably lead to increasing numbers of PNS observations.

## RESULTS

Thirty-five of the PNS cases (85%) were associated with a cSCC, four with a BCC (10%; one with squamous metaplasia) and two (5%) with another KSC type (trichilemmal carcinoma & pilomatrixoma; **Table 1**).

Six distinct PNS entities were reported (**Table 1**). The most frequent PNS, affecting 32/41 KSC patients was malignancy-associated hypercalcemia (MAH). MAH was primarily associated with cSCC (30/35 cSCC cases) and in five cases was accompanied by leukocytosis (hypercalcemia-leukocytosis syndrome). Hypercalcemia was severe (calcium serum level >14.0 mg/dL) in most (19/32, 60%), cases. Parathormone related protein (PTHrP) was increased in 20/21 patients with available data.

Other PNS included anemia (four patients, two of them with a pure red cell aplasia), Bazex syndrome (affecting two cSCC cases) and three other syndromes (antiphospholipid syndrome, inflammatory arthralgias and neuropathy, one case of each; **Table 1**). Notably, different KSC tended to associate with different PNS, so KSC of squamous phenotype with MAH and BCC with anemia.

In most cases (38/41 patients) PNS was diagnosed either concurrently or after the KSC diagnosis. A KSC predisposing condition, local or syndromic (genodermatosis), was reported in >70% of the present PNS cases with relevant information (23/32; **Table 1**). Finally, in most of the patients with available information (25/38 cases) the PNS resolved after KSC treatment.

Keratinocyte skin cancer	BCC (N=4)	SCC (N=35)	Other (N=2)	Total (N=41)
<b>Sex</b>				
Male	2	30	2	34
Female	2	5	0	7
<b>Localization</b>				
Head / neck	2	3	2	7
Trunk	2	17	0	19
Extremities	0	14	0	14
N/A	0	1	0	1
<b>PNS</b>				
MAH / HHM	0	30	2	32
Anemia	3	1	0	4
Bazex syndrome	0	2	0	2
Other	1	2	0	3
<b>Timing of PNS</b>				
before	0	3	0	3
simultaneously	1	19	2	22
after	3	13	0	16
<b>Primary</b>				
No	1	20	0	21
Yes	2	13	2	17
N/A	1	2	0	3
<b>Recurrence</b>				
No	2	23	2	27
Yes	1	10	0	11
N/A	1	2	0	3
<b>Metastases</b>				
No	3	15	2	20
Yes	1	16	0	17
N/A	0	4	0	4
<b>Genodermatosis<sup>1</sup></b>				
No	2	7	0	9
Yes	0	22	1	23
N/A	2	6	1	9
<b>Acquired</b>				
No	0	4	0	4
Yes	0	18	1	19
<b>Predilection</b>				
Scar/Ulcus	0	8	1	9
(burn) Scar	0	5	1	6
Ulcus	0	3	0	3
Hidradenitis suppurativa	0	8	0	8
Arsenic	0	1	0	1
Lymphedema	0	1	0	1
<b>Resolution</b>				
Yes	2	21	2	25
No	1	12	0	13
N/A	1	2	0	3

**Table 1.** Paraneoplastic syndromes in patients with keratinocyte skin cancer: Compilation of clinical features.

## REFERENCES

1. Bilynsky BT, Dzhus MB, Litvinyak RI. Exp Oncol 2015; 37: 82-8.