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Second primary malignancies in blastic plasmacytoid dendritic cell neoplasm: A national database study

To the Editor: Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is an aggressive cutaneous lymphoma.[1] Risk of second primary malignancies (SPMs) in leukemias/lymphomas with cutaneous involvement is a knowledge gap for dermatologists. We used the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database to determine SPM risk in patients with initial BPDCN and assess the results against its classification as a myeloid-derived malignancy.[2]

SEER compiles cancer incidence and survival data from 34.6% of the US population.[3] Initial BPDCN cases (1973-2016) were extracted via International Classification of Diseases for Oncology, Third Edition, histology code 9727/3 (blastic plasmacytoid dendritic cell neoplasm). Standardized incidence ratios (SIRs) and excess absolute risks (EARs) were computed for all SPMs relative to a control population matched by sex, race (white/unknown, black, other), age group (5-year interval), and calendar year (5-year interval). EAR was calculated per 10,000 individuals. *P* values of less than .05 were considered statistically significant.

We extracted 932 patients with BPDCN with a mean age of 32.06 years (±23.69) and follow-up of 125.37 months (±128.81). Of these, 43 patients (4.61%) developed SPMs, representing an increased risk compared to the control population (SIR, 1.43; 95% confidence interval [CI], 1.03-1.92; EAR, 13.57). Site-specific analysis is displayed in Table I. Compared to the control population, patients with BPDCN have significantly increased risk of acute myeloid leukemia (SIR, 27.68; 95% CI, 11.13-56.04; EAR, 7.18) and acute monocytic leukemia (SIR, 62.14; 95% CI, 1.57-346.25; EAR, 1.05). Additionally, these patients have an increased risk of thyroid SPMs (SIR, 10.17; 95% CI, 4.39-20.04; EAR, 7.68).

Percentage-wise, patients with initial BPDCN have a relatively low incidence of SPMs (4.61%). Nevertheless, patients with BPDCN still have a significant increase in SPMs overall, excluding nonmelanoma skin cancer, driven by thyroid and nonlymphocytic leukemia SPMs. Latency analysis showed risk of thyroid SPMs longer than 1 year from BPDCN diagnosis, arguing against an incidental/concurrent finding (Table II). We postulate this risk is due to treatment-related sequelae, such as chemotherapy and radiation. The increased risk of nonlymphocytic leukemia SPMs suggests a shared etiology; however, progression of BPDCN to a leukemic phase is also possible.

There is a notable lack of lymphoid-origin SPMs, which supports the current 2008 World Health Organization classification of BPDCN as a subtype of acute myeloid leukemias and related precursor neoplasms.[2] BPDCN had previously been considered a blastic natural killer cell lymphoma but was reclassified based on its plasmacytoid dendritic cell (pDC) origin; however, pDC development is a topic of ongoing research. Recently, Fernandes et al[4] demonstrated the dual origin of pDCs, with the

Table I. Site-specific second primary malignancy risk*

Second cancer site	O	O/E	95% CI	EAR
All sites	43	1.43†	1.03-1.92	13.57
All sites excluding nonmelanoma skin	43	1.42†	1.03-1.92	13.70
All solid tumors	31	1.16	0.79-1.65	4.65
Oral cavity and pharynx	2	2.40	0.29-8.68	1.24
Digestive system	5	0.93	0.30-2.16	−0.41
Respiratory system	2	0.49	0.06-1.78	−2.19
Bones and joints	1	10.41	0.26-58.01	0.96
Soft tissue including heart	0	0	0-15.98	−0.52
Skin excluding basal and squamous	0	0	0-2.22	−1.77
Melanoma of the skin	0	0	0-2.40	−1.64
Other nonepithelial skin	0	0	0-29.83	−0.13
Breast	5	1.34	0.43-3.12	1.34
Female breast	5	1.35	0.44-3.15	1.38
Male breast	0	0	0-102.49	−0.04
Female genital system	1	0.66	0.02-3.68	−0.55
Male genital system	4	0.75	0.21-1.93	−1.40
Urinary system	2	0.88	0.11-3.18	−0.29
Urinary bladder	2	1.51	0.18-5.45	0.72
Kidney and renal pelvis	0	0	0-4.13	−0.95
Renal pelvis, ureter, and other urinary organs	0	0	0-33.22	−0.12
Kidney	0	0	0-4.41	−0.89
Renal pelvis	0	0	0-66.46	−0.06
Ureter	0	0	0-105.70	−0.04
Other urinary organs	0	0	0-178.56	−0.02
Eye and orbit	0	0	0-64.94	−0.06
Brain and other nervous system	1	1.87	0.05-10.40	0.49
Brain	1	1.98	0.05-11.06	0.53
Cranial nerves/other nervous system	0	0	0-114.97	−0.03
Endocrine system	8	9.56†	4.13-18.83	7.62
Thyroid	8	10.17†	4.39-20.04	7.68
Thymus, adrenal gland, and other endocrine	0	0	0-72.86	−0.05
All lymphatic and hematopoietic diseases	11	3.75†	1.87-6.71	8.58
Lymphoma	1	0.60	0.02-3.35	−0.71
Hodgkin	0	0	0-11.50	−0.34
Hodgkin: nodal	0	0	0-11.77	−0.33
Hodgkin: extranodal	0	0	0-494.65	−0.01
NHL	1	0.74	0.02-4.15	−0.37
NHL: nodal	1	1.11	0.03-6.18	0.10
NHL: extranodal	0	0	0-8.35	−0.47
Myeloma	0	0	0-10.20	−0.38
Leukemia	10	11.01†	5.28-20.26	9.67
Lymphocytic leukemia	1	2.21	0.06-12.34	0.58
Acute lymphocytic leukemia	0	0	0-33.84	−0.12
Chronic lymphocytic leukemia	1	3.26	0.08-18.16	0.74
Other lymphocytic leukemia	0	0	0-102.94	−0.04
Nonlymphocytic leukemia	9	19.73†	9.02-36.45	9.09
Acute nonlymphocytic leukemia	8	27.25†	11.77-53.70	8.20
Myeloid and monocytic leukemia	8	19.56†	8.45-38.55	8.08
Acute myeloid leukemia	7	27.68†	11.13-56.04	7.18
Acute monocytic leukemia	1	62.14†	1.57-346.25	1.05
Chronic myeloid leukemia	0	0	0-28.80	−0.14
Other myeloid/monocytic leukemia	0	0	0-308.98	−0.01
Other leukemia	1	21.18	0.54-118.00	1.01
Other acute leukemia	0	0	0-150.02	−0.03
Aleukemic, subleukemic, and NOS	1	44.19†	1.12-246.23	1.04

Continued

Table I. Cont'd

Second cancer site	O	O/E	95% CI	EAR
Mesothelioma	0	0	0-59.47	−0.07
Kaposi sarcoma	0	0	0-23.87	−0.16
Miscellaneous	1	1.81	0.05-10.07	0.48

CI, Confidence interval; *E*, expected; *EAR*, excess attributable risk; *N/A*, not applicable; *NHL*, non-Hodgkin lymphoma; *NOS*, not otherwise specified; *O*, observed.

*Site-specific standardized incidence ratios and excess absolute risks of second primary malignancies in patients with previous blastic plasmacytoid dendritic cell neoplasm.

†$P < .05$.

Table II. Second primary risk by latency*

	Time since diagnosis, mo			
	2-11	12-59	60-119	120+
Cancer site	O O/E (95% CI) EAR	O O/E (95% CI) EAR	O O/E (95% CI) EAR	O O/E (95% CI) EAR
All sites	2 0.76 (0.09-2.7) −9.40	14 2.14† (1.17-3.60) 34.48	2 0.38 (0.05-1.35) −15.97	25 1.59† (1.03-2.34) 20.71
All sites excluding nonmelanoma skin	2 0.76 (0.09-2.75) −9.26	14 2.15† (1.18-3.61) 34.60	2 0.38 (0.05-1.36) −15.87	25 1.59† (1.03-2.35) 20.86
Thyroid	0 0 (0-114.61) −0.48	2 18.67† (2.26-67.45) 8.74	1 7.73 (0.20-43.07) 4.17	5 9.66† (3.14-22.53) 10.03
All lymphatic and hematopoietic diseases	0 0 (0-15.10) −3.61	8 12.76† (5.51-25.14) 34.05	0 0 (0-6.86) −2.58	3 1.97 (0.41-5.75) 3.30
Leukemia	0 0 (0-43.47) −1.26	8 38.12† (16.46-75.11) 35.97	0 0 (0-22.15) −0.80	2 4.48 (0.54-16.18) 3.48
Nonlymphocytic leukemia	0 0 (0-89.92) −0.61	8 78.93† (34.07-155.51) 36.48	0 0 (0-43.57) −0.41	1 4.36 (0.11-24.32) 1.72
Acute nonlymphocytic leukemia	0 0 (0-140.00) −0.39	7 106.43† (42.79-219.29) 32.08	0 0 (0-66.84) −0.26	1 6.84 (0.17-38.11) 1.91
Myeloid and monocytic leukemia	0 0 (0-104.99) −0.52	7 79.56† (31.99-163.93) 31.92	0 0 (0-49.28) −0.36	1 4.74 (0.12-26.41) 1.77
Acute myeloid leukemia	0 0 (0-172.08) −0.32	6 110.29† (40.48-240.06) 27.46	0 0 (0-78.98) −0.22	1 7.67 (0.19-42.76) 1.95
Acute monocytic leukemia	0 0 (0-2413.39) −0.02	1 274.43† (6.95-1529.05) 4.60	0 0 (0-1144.08) −0.02	0 0 (0-479.39) −0.02
Aleukemic, subleukemic, NOS	0 0 (0-1472.62) −0.04	1 176.84† (4.48-985.28) 4.59	0 0 (0-810.89) −0.02	0 0 (0-371.91) −0.02

CI, Confidence interval; *E*, expected; *EAR*, excess attributable risk; *O*, observed.

*Standardized incidence ratios and excess absolute risks of secondary malignancy distributed by time from diagnosis of blastic plasmacytoid dendritic cell neoplasm.

†$P < .05$.

majority of pDCs developing from interleukin 7 receptor^{+} lymphoid progenitor cells and a minor population of myeloid-derived pDC-like cells. Both groups were able to secrete type 1 interferons, but only myeloid-derived pDCs had the ability to process and present antigens. The lack of lymphoid-origin SPMs in our study supports the current myeloid classification of BPDCN.

Limitations include a retrospective design, coding errors, and inability to adjust for tumor characteristics, treatment, lifestyle/modifiable risk factors, and socioeconomic status.

Overall, our study's findings may help in the surveillance of patients with BPDCN, especially as new, lifespan-increasing treatments such as tagraxofusp become available.

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Merkel cell carcinoma of lymph nodes without a skin primary tumor: A potential metastatic neoplasia associated with a brisk immune response

To the Editor: Merkel cell carcinoma (MCC) is a rare neuroendocrine cutaneous carcinoma frequently caused by Merkel cell polyomavirus. In 10% of cases, MCC presents as lymph node metastasis (LNM) without a primary skin tumor (MCCWOP).[1] We and others[1] confirmed that MCCWOPs share a common phenotype with their cutaneous counterparts. However, whether MCCWOP constitutes an intranodal primitive neoplasia or a nodal metastasis from an occult or totally regressive skin MCC remains unknown.

The metastatic process is related to the epithelial-mesenchymal transition (EMT) characterized by a loss of epithelial markers such as E-cadherin and acquisition of a mesenchymal phenotype, with expression of N-cadherin or vimentin.[2] In addition, zinc finger E-box binding homeobox 1 (ZEB1)[3] is a crucial determinant of EMT. We hypothesized that investigating EMT markers in MCCWOP would help determine whether they constitute a primary neoplasia or a metastatic process. Expression levels of 4 EMT markers were evaluated by immunohistochemistry (Supplemental Methods and Supplemental Fig 1; available via Mendeley at https://data.mendeley.com/datasets/sn964fs2dp/draft?a=d6fc7ff0-f4d7-40f2-9658-f4cbdb7b0cd1) in 60 cutaneous primary MCCs, 18 LNMs from cutaneous MCCs, and 15 MCCWOPs. In the whole cohort (N = 93), loss of E-cadherin, aberrant expression of N-cadherin and vimentin, and expression of ZEB1 were observed in 91% (n = 82), 88% (n = 75), 6% (n = 5), and 74.5% (n = 61) of interpretable cases, respectively (Supplemental Tables I and II and Supplemental Fig 2; available via Mendeley at https://data.mendeley.com/datasets/sn964fs2dp/draft?a=d6fc7ff0-f4d7-40f2-9658-f4cbdb7b0cd1). Among the 78 MCC cases with an identified primary tumor, only ZEB1 harbored a significant differential expression between primary tumors and LNM (P = .047) and was therefore considered as a surrogate of metastatic process in MCC. As such, 74% of the LNMs from cutaneous MCCs (n = 11/15) but only 36% of primary tumors (n = 19/52) showed high and diffuse expression of ZEB1 (score 2) (P = .017). We found a similar pattern of ZEB1 (score 2) in 67% of MCCWOP cases (n = 10/15) (Table I and Fig 1), suggesting that MCCWOPs result from a metastatic process. Such a scenario would therefore imply a complete regression of a skin primary tumor, as a result of an efficient antitumoral immune response.[4] We investigated this hypothesis