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Outcomes in patients with extramammary Paget disease with brain metastasis: A retrospective analysis

To the Editor: Invasive extramammary Paget disease (EMPD) is an aggressive skin adenocarcinoma that metastasizes to regional lymph nodes (LNs), leading to subsequent distant LN, lung, liver, or bone metastasis. However, the prognosis of brain metastasis of EMPD remains elusive because of the paucity of reports.[1-5] Recently, we examined 8 cases of brain metastasis during the follow-up of patients with advanced EMPD. Here, we retrospectively analyzed the impact of brain metastasis on the prognosis of distant metastatic EMPD.

This study included 35 patients with distant metastatic EMPD who were treated at our department between April 2011 and March 2020; their clinical records were retrospectively reviewed. Overall survival (OS) and local control rates of brain metastasis were evaluated from the first day the indicated metastases were detected. This study was approved by the Ethics Committee of Keio University School of Medicine, and the protocol conformed to the ethical guidelines of the Declaration of Helsinki.

At study baseline, 31 of 35 (88.5%) patients had distant LN metastasis, and the remaining 4 (11.5%) had lung, liver, or bone metastasis (excluding the brain; hereafter referred to as *visceral metastasis*) (Table I). Among 31 patients with distant LN metastasis, 6 and 11 patients developed brain and visceral metastasis, respectively. Among 4 patients with visceral metastasis, 2 patients developed brain metastasis. Collectively, 8 (22.9%) and 15 (42.9%) of 35 patients with EMPD with distant metastasis developed brain and visceral metastases, respectively. All 8 patients

Table I. Characteristics of the study patients

Characteristics	All patients (N = 35)		Distant LN metastasis (n = 31)		Brain metastasis (n = 8)		Visceral metastasis* (n = 15)	
Sex, n								
Male	25		21		7		13	
Female	10		10		1		2	
Age, y								
Median (range)	68.0 (48-83)		68.0 (48-83)		66.5 (53-70)		67.0 (53-78)	
Metastatic sites, n	**Baseline**	**Final**	**Baseline**	**Final**	**Baseline**	**Final**	**Baseline**	**Final**
Distant LN only	31	15	31	15	0	0	0	0
Brain only	0	0	0	0	0	0	0	0
Visceral only	4	2	0	0	0	0	4	2
Distant LN + brain	0	5	0	5	0	5	0	0
Distant LN + visceral	0	10	0	10	0	0	0	10
Brain + visceral	0	2	0	0	0	2	0	2
Distant LN + brain + visceral	0	1	0	1	0	1	0	1
Follow-up, mo, median (range)	20.7 (0.8-64.4)		24.4 (0.8-64.4)		12.1 (3.7-18.6)		10.7 (0.8-24.2)	
OS, mo, median	NR		NR		NR		11.9	
1-year survival rate, %	88.2		93.5		83.3		46.2	
P value (vs distant LN metastasis)	—		—		.64		.0003	
P value (vs brain metastasis)	—		.64		—		.07	

LN, Lymph node; *NR*, not reached; *OS*, overall survival.
*Liver, lung, or bone metastases are referred to as *visceral metastases*.

Table II. Characteristics of patients with brain metastasis

Case	Age, y, Sex	Brain metastases, n	Metastatic sites		Treatment	Types of chemotherapy	Local recurrence	OS after distant metastasis, mo	OS after brain metastasis, mo
			Baseline	Final					
1	70, M	1	Distant LN	Distant LN, brain	Chemotherapy and SRT	PET	No	31.9+	12.4+
2	69, M	1	Distant LN	Distant LN, brain	Chemotherapy and SRS	PET	No	38.2+	7.6+
3	53, M	1	Lung	Lung, brain	Chemotherapy	PET	No	17.5+	11.9+
4	66, F	3	Distant LN	Distant LN, brain	Chemotherapy and SRT	PET	No	25.9+	18.6+
5	66, M	8	Distant LN	Distant LN, brain	Chemotherapy and SRT	Docetaxel and tegafur/gimeracil/oteracil	No	24.4+	12.3+
6	68, M	>10	Distant LN	Distant LN, brain	Chemotherapy and WBRT	Trastuzumab and docetaxel	No	17.2+	3.7+
7	63, M	5	Liver	Liver, bone, brain	Chemotherapy and WBRT	Docetaxel	No	15.0	11.5
8	67, M	6	Distant LN	Distant LN, liver, brain	Chemotherapy, SRT, and SR	Docetaxel	Yes	28.5+	16.9+
Median	66.5	4	—	—	—	—	LCR: 88%	25.2+	12.1+

+, Ongoing response; *F*, female; *LCR*, local control rate; *LN*, lymph node; *M*, male; *OS*, overall survival; *PET*, cisplatin, epirubicin, and paclitaxel; *SR*, surgical resection; *SRS*, stereotactic radiosurgery; *SRT*, stereotactic radiotherapy; *WBRT*, whole brain radiotherapy.

with brain metastasis received chemotherapy, and 7 of the 8 additionally received radiotherapy, such as stereotactic radiotherapy or whole-brain radiotherapy. At a median follow-up period of 12.1 months (range, 3.7-18.6 months), only 1 patient developed recurrence of brain metastasis, with a local control rate of 88% (Table II).

Distant LN and visceral metastases preceded brain metastasis by a median of 12.8 (range, 3.5-30.6 months) and 4.5 months (range, 3.5-5.5 months), respectively. The 1-year OS rates of patients with distant LN, brain, and visceral metastases were 93.5%, 83.3%, and 46.2%, respectively. Until the end of follow-up, all patients without visceral metastasis were alive. Furthermore, patients with distant LN metastasis ($P = .0003$) and those with brain metastasis ($P = .07$) had longer OS rates than did those with visceral metastasis.

Brain metastasis had not been recognized in patients with EMPD until recently. However, Yamashita et al[5] identified 5 patients with brain metastasis (22.7%) during the follow-up of patients with invasive EMPD, in line with our results (22.9%).[5] These results suggest that brain metastasis is a common metastatic site in EMPD.

Intriguingly, the majority of the patients with EMPD with brain metastasis did not develop disease progression and were able to continue the same regimen, whereas most of those with visceral metastasis required switching to different regimens because of disease progression. Thus, OS rates were better for patients with brain metastasis than for those with visceral metastasis. In conclusion, our results indicate that routine follow-up for brain metastasis using magnetic resonance imaging or radiation therapy in combination with chemotherapy could enhance the quality of life and prognosis of patients with EMPD with brain metastasis.

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Biotin interference in routine laboratory tests: A bibliometric analysis

To the Editor: Biotin (vitamin B_7), a cofactor in metabolic pathways, is often recommended to promote hair, skin, and nail growth. Biotin can interfere with routine laboratory tests that use biotin-streptavidin binding,[1] leading to misdiagnosis and even death.[2] A US Food and Drug Administration (FDA) warning on biotin interference was issued in 2017.[3] In a survey-based study, 60% of physicians were knowledgeable about biotin interference with thyroid/troponin tests, with most unaware of interactions with hepatitis, HIV, beta-human chorionic gonadotropin and vitamin D tests (S.R. Lipner, unpublished data, April 2020). This study aimed to characterize the biotin laboratory interference literature and frequency of reported laboratory interactions.

Web of Science (WOS) and SCOPUS were searched for term *biotin interference* alone and in combination with *troponin*, *thyroid*, *HCG*, *hepatitis*, *HIV*, and *vitamin D*. Results were analyzed for publications per year, research subject, Altmetric score, citation averages, and *h*-indices.

The search for *biotin interference* yielded 101 and 99 results in WOS and SCOPUS, respectively, with greater than 90% overlap and 109 unique publications. *Biotin interference* and *thyroid* was most frequent (71), followed by *troponin* (24) (Table I). Case reports/series showed that thyroid, parathyroid hormone, and troponin interference affected 39 (8 in patients with multiple sclerosis taking an average dose of 300 mg/day), 3, and 3 unique patients, respectively.

Biotin interference was first described in 1995, with a sharp increase in publications in 2017. Search results were most often published in clinical laboratory technology and biochemistry journals (Table I). The *h*-index, a metric of the cumulative impact of articles weighted to correct for highly cited articles, was 15 for the term *biotin interference*, 6 for *biotin interference* and *troponin*, and 10 for *biotin interference* and *thyroid* (Table I).

The top 20 most cited *biotin interference* publications were cited 11 to 62 times, with Altmetric scores, a measure of media attention of a publication, of 1 to 72. The most common theme was thyroid disease, in 6 of 20 (30%) (Table II). On average, publications with more citations did not correlate with higher Altmetric scores.

Our study shows that there were few publications on biotin interference before 2017, a spike in 2017 (likely prompting the 2017 FDA warning), and low *h*-index (<20) and media attention scores. These data are consistent with an Altmetric study on biotin literature after the FDA alert, showing that this warning was rarely mentioned and generally not published in high-impact journals.[4] Furthermore, the most highly cited articles were published in biochemistry or laboratory medicine journals, as opposed to medicine journals. Therefore, these biotin articles are more likely to be read by basic science researchers rather than dermatologists.

This bibliometric analysis of the biotin literature showed that there were relatively few search results and relatively low impact of publications regarding laboratory interference. Taken together, our study may explain the lack of physician awareness of the FDA warning regarding the risks of recommending biotin. Therefore, there is a need for more literature targeted toward dermatologists detailing the potential interference of biotin on various assays, especially those besides thyroid panels and