Original Investigation

Association of Histologic Regression in Primary Melanoma With Sentinel Lymph Node Status
A Systematic Review and Meta-analysis

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Editorial page 1291

IMPORTANCE The prognostic significance of regression in primary melanoma has been debated for many years. There is no consensus regarding the need for sentinel lymph node (SLN) biopsy when regression is present within the primary tumor.

OBJECTIVE To review the evidence that regression may affect SLN status.

DATA SOURCES A systematic review was performed by searching in MEDLINE, Scopus, and the Cochrane Library from January 1, 1990, through June 2014.

STUDY SELECTION All studies that reported an odds ratio (OR) or data on expected and observed cases of SLN positivity and histologic regression were included.

DATA EXTRACTION AND SYNTHESIS Primary random-effects meta-analyses were used to summarize ORs of SLN positivity and histologic regression. Heterogeneity was assessed using the χ^2 test and I^2 statistic. To assess the potential bias of small studies, we used funnel plots, the Begg rank correlation test, and the Egger weighted linear regression test. The methodologic quality of the studies was assessed according to the Strengthening of Reporting of Observational studies in Epidemiology (STROBE) checklist, and 2 different meta-analyses were performed based on those criteria.

MAIN OUTCOMES AND MEASURES Summary ORs of histologic regression of primary melanoma and SLN status.

RESULTS Of the 1509 citations found in the search, 94 articles were reviewed, and 14 studies comprising 10 098 patients were included in the analysis. In the combined 14 studies, patients with regression had a lower likelihood to have SLN positivity (OR, 0.56; 95% CI, 0.41-0.77) than patients without regression. On the basis of study quality, we found that patients with regression enrolled in high-quality studies had a lower likelihood to have SLN positivity (OR, 0.48; 95% CI, 0.32-0.72) compared with results of low-quality studies (OR, 0.73; 95% CI, 0.53-1.00). Examination of the funnel plot did not provide evidence of publication bias.

CONCLUSIONS AND RELEVANCE The results of this analysis showed that the risk of SLN positivity was significantly lower in patients with histologic regression compared with those without. Regression may be used in these cases to make a selection of which patients should be the most appropriate for this procedure.

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Histologic regression in melanoma is defined as an area within the tumor in which neoplastic cells have disappeared or become reduced in number from the dermis (and occasionally from the epidermis) and have been substituted by fibrosis with accompanying melanophages, new vessels, and a variable inflammatory infiltrate.[1,2] Regression is found in melanoma with a frequency that ranges from 10% to 35%.[3] The prognostic significance of regression in primary melanoma has been debated for many years.[4] The potential poor prognosis associated with regression is that the disappearance of a portion of the tumor may lead to an underestimation of the original Breslow thickness. It is therefore difficult to accurately assess prognosis and also whether sentinel lymph node biopsy (SLNB) should be used to assess thickness, since it might no longer be accurate.[5-8]

Sentinel lymph node (SLN) status is the most important prognostic factor in intermediate and thick melanomas.[9,10] There is no consensus regarding the need for SLNB when regression is present within the primary tumor.

Some authors[5,11] reported that regression is associated with a higher risk of developing lymph node metastasis. On the contrary, White et al[12] reported that in thin melanomas (<1 mm), the presence of regression is associated with a lower likelihood of positive SLN findings. Furthermore, other studies have shown that regression does not increase the risk of metastases[1,7] and does not negatively affect prognosis.[4]

A consensus survey carried out in France demonstrated that guidelines for most melanoma centers advocate SLNB in the case of Breslow thickness greater than 1.0 mm (76%) and/or ulceration of the primary melanoma (38%) and/or histologic regression of the primary melanoma (24%).[6] Other countries do not have regression as a selection criteria for SLNB.

Since 2009, SLNB has been recommended for intermediate-thickness (1- to 4-mm) melanomas.[13] However, it has recently been extended to thinner lesions showing mitosis.[14] Given the lack of evidence-based guidelines by which to stratify thin melanomas for this procedure, the selection criteria in fact vary widely between institutions and countries. To review the evidence that regression may affect SLN status, we conducted a meta-analysis of published literature to provide a more objective estimate of the incidence of SLN positivity in patients with histologic regression in primary melanoma tumors.

Methods

We carried out this review in accordance with PRISMA (Preferred Reporting Items for Systematic review and Meta-analysis guidelines).[15]

Search Strategy, Eligibility Criteria, and Study Selection

A systematic review of original articles and abstracts analyzing the SLN status of patients with histologic regression of primary melanoma was performed by searching in MEDLINE, Scopus, and the Cochrane Library from January 1, 1990, through June 2014. The search strategy included the following keywords in various combinations: "melanoma," "lymph nodes," "sentinel lymph node biopsy," "histologic regression"; 1509 citations were reported in total. In addition we reviewed articles and relevant reviews to locate publications missed by the database searches. Two authors (S.R. and E.B.) independently assessed the eligibility of studies. Any disagreement was settled by consensus, including a third and fourth investigator (S.O.-A. and P.Q.). The article title and abstract were used for initial screening, followed by review of the full text. There was no restriction criterion on the number of patients enrolled in the study. Only original manuscripts in English language were included. Searches were supplemented by scanning bibliographies of included articles. We excluded articles that reported no data, such as review articles and editorials. If duplicate data were present in separate publications, we included the publication with the larger amount of data or the more recent. All articles that reported data on SLN status and histologic regression in patients with melanoma were eligible for inclusion.

Data Extraction

We used a data extraction form based on the Cochrane Consumers and Communication Review Group data examination template.[16] For each study selected, the following data were extracted: journal, year, study design, number of patients, age, sex, melanoma thickness, ulceration, histologic regression, SLN status.

Assessment of Study Quality

The quality of studies included in the meta-analysis, in terms of design, is of utmost importance because combining study results of poor quality may lead to biases and therefore misleading results. Study quality may be used for explaining the heterogeneity of the study outcomes; however, no consensus exists regarding the assessment of statistical analysis. For each article, study quality was determined by blinded review by 2 independent reviewers (S.R. and P.Q.). To avoid selection bias, no study was excluded based on the quality score alone in the assessment of the overall effect. The methodologic quality of the studies was assessed according to the Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) checklist.[17] The STROBE statement consists of a checklist of 22 items that should be addressed in reports of observational studies.

Statistical Analysis

To integrate previous findings on this topic, we performed a meta-analysis of published literature to provide an estimate of the incidence of SLN positivity in patients with melanoma with evidence of regression in the tumor. Because studies were found to be heterogeneous, summary odds ratios (ORs) with corresponding 95% CIs were calculated using random-effects modeling. Publication bias was assessed through the construction of a funnel plot for the primary end point, as well as with the Begg and Mazumdar adjusted rank correlation method. To address the heterogeneity of the studies, we therefore performed subgroup analyses by considering the quality of the studies assessed through the STROBE checklist. Nine studies scored more than 75% of the STROBE criteria,[8,18-25] while 5 studies fulfilled less than 75% of those criteria.[26-30]

Statistical analyses were performed using Stata statistical software, version 13.0 (StataCorp LP).

Results

Characteristics of Included Studies

The initial search resulted in 1509 citations (**Figure 1**). The title and abstract of each retrieved publication was reviewed to confirm that the article included data on SLN positivity and regression melanoma tumors. In the event that this approach was not informative, the full article was retrieved and further reviewed. This process resulted in the selection of 94 studies. Of these, 74 were eventually excluded from this analysis because they did not showed clear results on SLN status in relation to regression. Five presented overlapping data from other studies so were also excluded. Fourteen studies[8,18-30] were therefore eligible for the inclusion in the systematic review and meta-analysis. Five of those reported data pooled from multiple centers (**Table**).[18,21,22,26,27]

Ultimately, 14 studies including a total of 10 098 patients were finally included. Sentinel lymph node inclusion criteria were clearly described in 9 studies.[8,19,21,22,26-30] From these 9 studies, regression was described as a selection criteria for SLNB in 4 of them.[8,21,29,30] Histologic description of regression was reported in 7 articles.[8,18,20,21,26,29,30] Presence of histologic regression in primary melanoma was reported in 10% to 51% of patients with negative SLNs and 35% or fewer with positive SLNs in 13 out of 14 studies[8,18-25,27-30]; only Tejera-Vaquerizo et al[26] did not describe crude values of distribution but reported only the OR of this association with a confidence interval.

Figure 1. Flowchart of Article Search and Inclusion

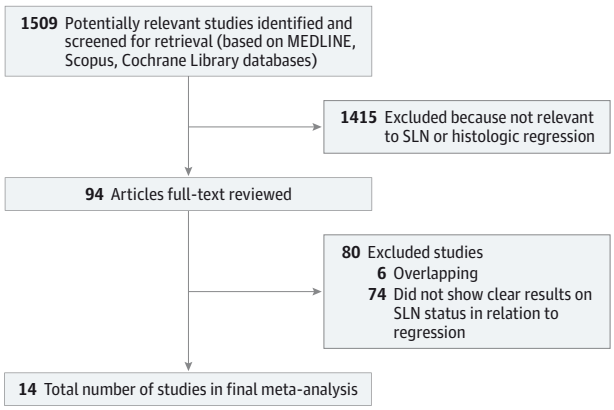


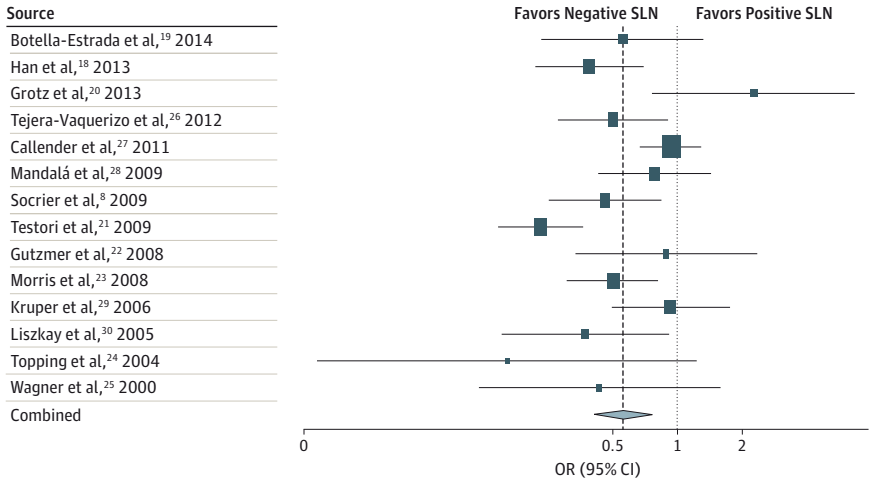
Table. Characteristics of the Included Studies

Source[a]	State/Study Name	Patients, No.	Breslow Depth, mm	SLN Status, No (%)			
				Negative		Positive	
				Regression	No Regression	Regression	No Regression
Botella-Estrada et al,[19] 2014	Spain	201	Not evaluable	45 (39)	116 (61)	7 (21)	33 (79)
Han et al,[18] 2013	Sentinel Lymph Node Working Group	1250	Median (range), 0.84 (0.09-1.00)	184 (23)	605 (77)	5 (11)	42 (89)
Grotz et al,[20] 2013	United States	250	Not evaluable	35 (19)	146 (81)	6 (35)	11 (65)
Tejera-Vaquerizo et al,[26] 2012	Spain	698	Not evaluable	Not evaluable	Not evaluable	Not evaluable	Not evaluable
Callender et al,[27] 2011	Sunbelt trial	2500	Not evaluable	211 (12)	1562 (88)	50 (11)	400 (89)
Mandalà et al,[28] 2009	Italy	404	Mean (SD), 1.3 (2.1)	86 (29)	209 (71)	17 (24)	53 (76)
Socrier et al,[8] 2009	France	397	Median (IQR), 1.8 (1.1-3.0)	79 (27)	215 (73)	15 (15)	88 (85)
Testori et al,[21] 2009	Italy	1313	Not evaluable	360 (39)	568 (61)	23 (13)	161 (77)
Gutzmer et al,[22] 2008	Germany	152	Median (range), 5.2 (4-18)	10 (14)	64 (86)	9 (12)	65 (88)
Morris et al,[23] 2008	United States	1349	mean: 1.5, no regression; 1.1, regression	198 (25)	597 (75)	21 (14)	127 (86)
Kruper et al,[29] 2006	United States	682	Median (range), 1.3 (0.2-18.0)	93 (16)	501 (84)	13 (15)	75 (85)
Liszkay et al,[30] 2005	Hungary	280	Mean: 2.41, no regression; 1.24, regression	68 (30)	155 (70)	6 (14)	37 (86)
Topping et al,[24] 2004	United Kingdom	347	Mean (SD), 2.04 (2.32)	27 (10)	259 (90)	0	61 (100)
Wagner et al,[25] 2000	United States	275	Median (range), 2.24 (0.20-14.00)	27 (13)	184 (87)	3 (6)	48 (94)

Abbreviations: IQR, interquartile range; SLN, sentinel lymph node.

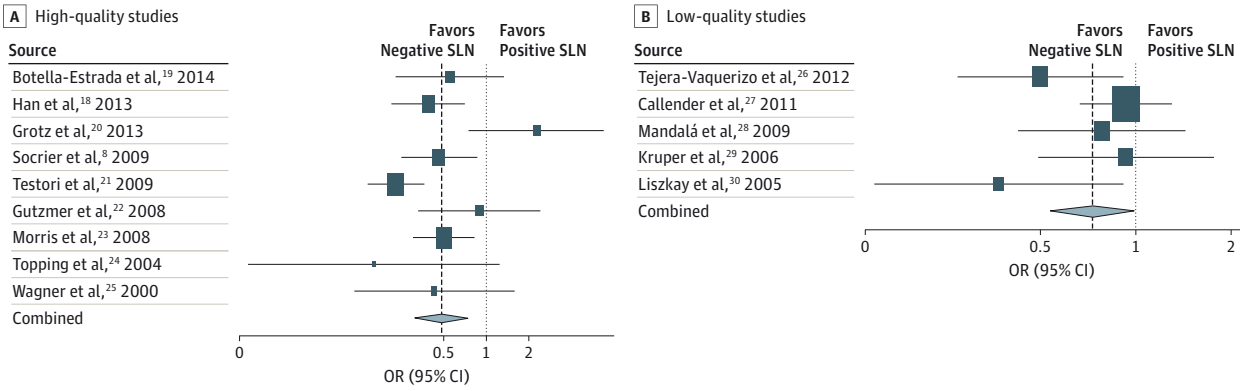
[a] All study designs were retrospective except for the study by Callender et al,[27] which was post hoc analyses of a trial. Most studies took place in a single center, with the following exceptions: the studies by Tejera-Vaquerizo et al[26] and Gutzmer et al[22] were carried out across 2 centers; those by Han et al,[18] Callender et al,[27] and Testori et al[21] were multicentric.

Figure 2. Likelihood in Patients With Melanoma of Positive Sentinel Lymph Node (SLN) Biopsy Findings



Illustrated are the standardized odds ratios (ORs) for the studies included in the meta-analysis. Patients with histologic regression of primary melanoma had a lower likelihood of SLN positivity (OR, 0.56; 95% CI, 0.41-0.77; darker dashed vertical line) than patients without regression.

Figure 3. Likelihood of Positive Sentinel Lymph Node (SLN) Biopsy Findings in Patients With Melanoma by Study Quality



Illustrated are the standardized odds ratios (ORs) for the high- and low-quality studies included in the meta-analysis. Patients with regression enrolled in high-quality studies had a lower likelihood of SLN positivity (OR, 0.48; 95% CI, 0.32-0.72; darker dashed vertical line) than similar patients enrolled in low-quality studies (OR, 0.73; 95% CI, 0.0.53-1.00; darker dashed vertical line).

All studies reported clinical data of the patients on sex and age. Among them, data on Breslow thickness that is the major prognostic factor in melanoma, were described as mean depth in 4 studies[22,25,28,30] and as median depth in 5.[8,18,22,23,27] In the remaining 6 articles,[19-21,24,26,29] Breslow thickness was reported as categorical cutoff. Ulceration distribution was described in all 14 articles.[8,18-30] Of the 14 analyzed reports, seven[8,20,23,26-28,30] declared the association between histologic regression and other demographic data or tumor variables. In particular, Grotz et al[20] showed that histologic regression was not associated with sex, age, Breslow thickness, ulceration, mitotic rate, satellitosis, or tumor-infiltrating lymphocytes. Tejera-Vaquerizo et al[26] showed that a lower rate of histologic regression was associated with fast-growth melanoma. Liszkay et al[30] demonstrated that tumors with histologic regression were associated to superficial spreading melanoma histotype, thinner lesions, and absence of ulceration. Also Socrier et al[8] observed that only 2% of melanoma lesions presented both regression and ulceration. In consideration of primary anatomic site, regression was significantly associated with primary melanoma located on the trunk in 3 studies.[23,27,30] In contrast, no significant association between anatomic site (trunk vs extremities) and regression was observed by Mandalà et al.[28]

Outcome of Meta-analysis

In the included 14 studies combined, patients with histologic regression of primary melanoma had a lower likelihood to have a SLN positivity (OR, 0.56; 95% CI, 0.41-0.77) than patients without regression (**Figure 2**). On the basis of study quality, we found that patients with regression enrolled in high-quality studies had a lower likelihood to have SLN positivity (OR, 0.48; 95% CI, 0.32-0.72) compared with those enrolled in low-quality studies (OR, 0.73; 95% CI, 0.53-1.00) (**Figure 3** and **Figure 4**). Examination of the funnel plot (Figure 4) did not provide evidence of publication bias. Similarly, there was no evidence of such bias for the sensitivity analysis. In fact, the

analysis shows that the points are evenly distributed and symmetrical, thus showing absence of bias and suggesting that the results of the studies are reliable. This evidence was confirmed by the results of the Begg and Mazumdar test (0.53 and 0.15 for the overall calculation for the high-quality studies and the low-quality studies, respectively; $P = .75$).

Discussion

In this systematic review and meta-analysis including 14 studies[8,18-30] and more than 10 000 patients, we found that histologic regression is a protective factor for SLN-positive status: patients with melanoma and regression had a lower likelihood of SLN positivity (OR, 0.56; 95% CI, 0.41-0.77) than patients without regression.

Clinical Significance

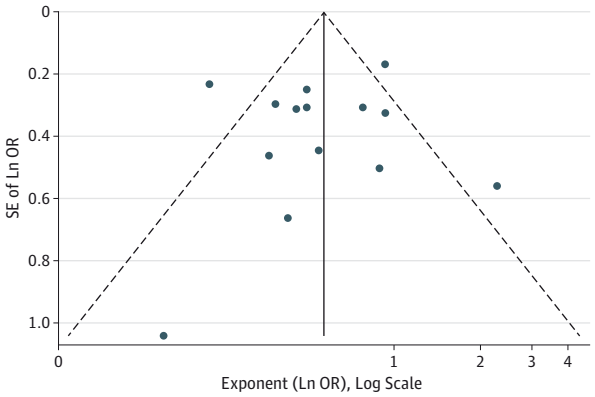
Histologic regression has traditionally been considered a marker of poor prognosis because it leads to an underestimation of melanoma thickness.[5-8] The introduction of SLNB has led to the evaluation of melanoma tumor thickness and ulceration for the selection of patients eligible for SLNB, and regression is a feature that has previously been evaluated.[5] Some studies have found that regression in melanoma does not increase the risk of lymphatic metastasis and therefore does not affect prognosis,[7,25,30,31] while other studies have reported that regression is associated with a poor prognosis, particularly in thin melanomas.[11] Our group has previously reported that regression plays a protective prognostic role in patients with melanoma (stage I-II AJCC).[4,32]

It can sometimes be difficult to decide if patients should undergo SLNB for tumors thinner than 1 mm.[4,10] Although the presence of mitosis is now among the inclusion criteria for SLNB, adding regression may provide extra prognostic value. To our knowledge, the current report represents the first meta-analysis to focus on the predictive value of histologic regression on SLN status in melanoma. We found that the risk of sentinel metastatic involvement was significantly lower in patients with histologic regression in melanoma tumors compared with those without regression.

Conflicting data are reported on prognostic value of histologic regression. Kaur et al[7] observed that SLN positivity was more common in tumors with regression than in those without. In contrast, Testori et al[21] suggest that regression should be considered a protective factor for SLN metastasis. Mandalà et al[28] did not observe any correlation between regression and SLN positivity. Similarly, Morris et al[23] showed that the presence of histologic regression in a primary melanoma predicted neither SLN positivity stratified by the Breslow thickness nor increased the risk of recurrence when compared with melanomas without regression. Melanoma is a strong immunogenic tumor. A strong host immunological response to the tumor is thought to be the cause of the tumor regression. It would therefore be expected that the presence of regression would confer survival advantage.

Nevertheless, it can be suggested that a host immunologic response to the tumor could be the basis of regression.

Figure 4. Funnel Plot of the Studies Included in the Meta-analysis



The funnel plot displays points (each representing an included study) that are evenly and symmetrically distributed, thus showing the absence of study bias and suggesting that the results of the studies are reliable. Ln indicates natural log; OR, odds ratio; SE, standard error.

This phenomenon therefore could reflect the power of the immunologic system against the primary tumor, and its presence should be considered prognostically favorable. Ma et al[33] showed that the immune profile of the primary melanoma could predict the SLN status and that the presence of primary tumor regression results from a T-cell immune response associated with a decreased risk of nodal progression. In particular, these authors describe a downregulation of the antitumor immunity in the positive SLN with an increase in regulatory T cells compared with the negative nonsentinel node from the same nodal basin. Furthermore, Ma et al[33] reported that primary tumor conventional dendritic cells and regression were protective against SLN metastasis.

Limitations

Significant heterogeneity existed among studies with respect to study quality characteristics, as confirmed by the Q statistic. Although random-effect modeling incorporates this heterogeneity, the possibility remains that the SLN positivity rate in each study is mediated by unmeasured factors, and the pooled SLN positivity rate may be misleading as a result. We could not adjust our pooled estimate for the effects of confounding through a formal metaregression because covariate information was not consistently reported in the published studies. The reliability of summary estimates is contingent on the quality of the studies pooled. Despite this, when random effects were evaluated in 2 subgroups of studies divided by quality based on the STROBE test, the protective role of regression was maintained. We found that patients with regression enrolled in high-quality studies had a lower likelihood of SLN positivity (OR, 0.48; 95% CI, 0.32-0.72) than similar patient enrolled in low-quality studies (OR, 0.73; 95% CI, 0.0.53-1.00). Although included studies met many of the a priori quality metrics, important deficiencies remained. Because the indication for SLNB and the ultimate outcomes of those with a positive result is very hard to assess in a randomized fashion, methodologic shortcomings are inevitable.

Another potential limitation is that the included studies may have had different definitions of histological regression, as sometimes the definition of this feature is discussed. Further studies and an international consensus regarding more reproducible evaluation of regression, such as the percentage of the lesions regressed (eg, 50%), would be needed to better characterize this feature.

Moreover, this study reviewed only observational, mostly retrospective studies reported in English. Most studies were also from a single institution. In some cases, multiple reports were published over time from the same institution, and considerable effort was expended to identify and use the most suitable report. It is possible, however, that some patients were excluded by our efforts to avoid duplicates in consecutive studies reported by the same group. Nevertheless, based on the number of patients reviewed in the present analysis, it is unlikely that missing these cases would have significantly affected the results.

These limitations underscore the need for standardized reporting of relevant covariates in future observational studies. From a methodologic perspective, *histologic regression* needs a worldwide consensus regarding the definition to give the possibility to further analyze this intriguing feature. All other prognostic factors should also be collected accurately. It has also been recommended that 2 investigators separately assess the regression histologically in primary melanoma specimens and that high interobserver agreement should be achieved.

Conclusions

The results of this meta-analysis may be useful when deciding to offer SLNB to patients with regressions of melanomas. It may help clinicians make a final selection of the most appropriate patients for this procedure.

ARTICLE INFORMATION

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Study concept and design: Ribero, Gualano, Osella-Abate, Fierro, Macripò, Sapino, Siliquini.
Acquisition, analysis, or interpretation of data: Ribero, Gualano, Osella-Abate, Scaioli, Bert, Sanlorenzo, Balagna, Sapino, Quaglino.
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Conflict of Interest Disclosures: None reported.

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NOTABLE NOTES

Smallpox, Anthrax, and the Historiography of Cutaneous Diseases

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The eradication of smallpox is one of the great success stories of modern medicine. As the clinical memory of smallpox fades from the imagination of both the public mind and the medical community, it is helpful to recall that in many ways even its distant past remains shrouded in mystery.

While it has been almost 40 years since the last known case of smallpox, the impact of this disease on the world population can hardly be overstated. In medieval Europe, it is estimated that almost a half million people died annually from this scourge, and survivors were left with a variety of permanent sequelae, including scarring and blindness.[1]

Robert Willan, the British physician and founder of modern dermatology, posthumously published *An Inquiry into the Antiquity of the Small-Pox, Measles, and Scarlet Fever*.[1] Willan presciently argued against the then-conventional wisdom that smallpox originated after the fall of the Roman Empire. Indeed, 18th-century authors, including De Hahn and Werlhoff, engaged in extensive debates on the etiology of this disease, with the chief argument against smallpox's antiquity being that the lack of a reliable description prior to the Persian physician (and alchemist) Rhazes' ninth century text suggested that it did not predate his time.

Willan's arguments in favor of smallpox's antiquity rested on several pillars: first, he undermined the silence-equals-absence argument by highlighting that ancient texts tended to conflate smallpox, measles, and plague. He then pointed out that some authors distinguished between loimos (plague) and a separate fiery disorder, anthrax (or *anthrakes*, from the Greek word meaning "fiery coal").[2] Moreover, the "anthrax" spread over the entire body; the eyes were prominently affected, leading to blindness; and the survivors did not experience the disease a second time—all clinical features entirely inconsistent with plague but entirely consistent with smallpox. Thus, Willan argued that "anthrax," as described in ancient Greek texts, actually referred to smallpox. He therefore posited that Hippocrates and other prominent ancient Greek physicians were not silent on the existence of smallpox; they simply referred to it by a different name and may have conflated it with other infectious diseases. Willan's efforts notably relied not only on medical writers but also on descriptions by Roman poets and philosophers from Philo to Livy.

A century after Willan's death, support for his theory of the antiquity of smallpox came from an unexpected source. The well-preserved mummy of Pharaoh Ramses V, who died in his 40s, was discovered. When closely examined, his body was noted to be covered in confluent vesicles—entirely consistent with the diagnosis of smallpox.[3]

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