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Warfarin-Associated Nonuremic Calciphylaxis

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IMPORTANCE Classic calciphylaxis associated with renal failure is a life-threatening disease. Warfarin-associated calciphylaxis without renal injury has been described, but whether it is a subset of classic calciphylaxis or a different entity remains unknown. We describe 1 case of warfarin-associated calciphylaxis, present data from 2 others from our institution, and review all cases of warfarin-associated calciphylaxis available in the literature. Our review indicates that warfarin-associated calciphylaxis is clinically and pathophysiologically distinct from classic calciphylaxis.

OBJECTIVE To review warfarin-associated calciphylaxis and determine its relationship to classic calciphylaxis.

DESIGN, SETTING, AND PARTICIPANTS We searched MEDLINE and Ovid without language or date restrictions for case reports of calciphylaxis from the inpatient setting using the terms "calciphylaxis and warfarin," "non-uremic calciphylaxis," and "nonuremic calciphylaxis." We defined nonuremic calciphylaxis as a histopathologic diagnosis of calciphylaxis without severe kidney disease (serum creatinine level >3 mg/dL; glomerular filtration rate <15 mL/min; acute kidney injury requiring dialysis; and renal transplantation).

EXPOSURES Each patient had been exposed to warfarin before the onset of calciphylaxis.

MAIN OUTCOMES AND MEASURES Patient data were abstracted from published reports. Original patient medical records were requested and reviewed when possible.

RESULTS We identified 18 patients with nonuremic calciphylaxis, 15 from the literature, and 3 from our institution. Patients were predominantly female (15 of 18 [83%]) with ages ranging from 19 to 86 years. Duration of warfarin therapy prior to calciphylaxis onset averaged 32 months. Lesions were usually located below the knees (in 12 of 18 [67%]). No cases reported elevated calcium-phosphate products (0 of 17 [0%]). Calcifications were most often noted in the tunica media (n = 8 [44%]) or in the vessel lumen and tunica intima (n = 7 [39%]). The most common treatments included substitution of heparin or low-molecular weight heparin for warfarin (n = 13 [72%]), intravenous sodium thiosulfate (n = 9 [50%]), and hyperbaric oxygen (n = 3 [17%]). The survival rate on hospital discharge was remarkably high, with 15 cases (83%) reporting full recovery and 3 cases ending in death.

CONCLUSIONS AND RELEVANCE Warfarin-associated calciphylaxis is distinct from classic calciphylaxis in pathogenesis, course, and, particularly, outcome. This finding should influence clinical management of the disease and informs targeted treatment of the disease.

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Calciphylaxis is a syndrome of cutaneous ischemic necrosis presenting as painful violaceous reticular patches or plaques that evolve into stellate ulcerations over the abdomen, thighs, and buttocks.[1,2] These lesions result from arteriolar calcification with subsequent thrombosis, a 2-step process described by Weenig[2] as the cutaneous equivalent of a myocardial infarction.

Calciphylaxis classically occurs with renal failure (calcific uremic arteriolopathy), but can also occur without kidney disease (nonuremic calciphylaxis), usually precipitated by hyperparathyroidism, liver disease, corticosteroids, malignant neoplasm, or warfarin.[1,3,4] We describe a case of warfarin-associated calciphylaxis, present data from 2 others from our institution, and review all cases of warfarin-associated calciphylaxis available in the literature. Our review indicates that warfarin-associated calciphylaxis is a distinct clinical subgroup with separate pathophysiologic characteristics and a favorable prognosis.

Key Points

Question Is warfarin-associated calciphylaxis a distinct disease when compared with classic calciphylaxis, and, if so, what are its features?

Findings In this review of reports of 18 patients with warfarin-associated calciphylaxis, 15 had used warfarin for an average of 32 months prior to calciphylaxis onset, and the most common treatments were substitution of heparin or low-molecular weight heparin for warfarin, intravenous sodium thiosulfate, and hyperbaric oxygen. Survival after hospital discharge was high with 15 cases (83%) reporting full recovery and 3 cases ending in death.

Meaning Warfarin-associated calciphylaxis is distinct from classic calciphylaxis in pathogenesis, course, and outcome.

Report of a Case

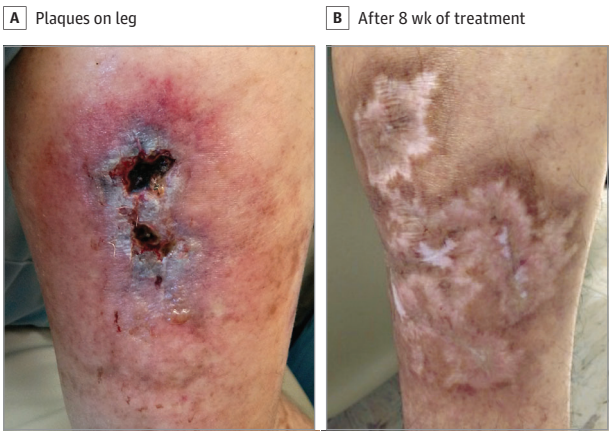
A woman in her 60s with hypertension, hyperlipidemia, rheumatoid arthritis, diabetes, and atrial fibrillation presented with 1-year history of livedo reticularis and new palpable purpura over her bilateral lower extremities. She did not have renal disease or hyperparathyroidism, but she had taken warfarin for 2 years. A biopsy specimen showed calcification of small- to medium-size vessels within the subcutis, fat necrosis, and neovascularization. Ten days later, the patient developed tender stellate ulcers with purpuric borders, surrounding fixed livedo, and retiform purpura on her right leg including and extending beyond the biopsy site (**Figure 1**). She was admitted to the hospital.

Laboratory data included a creatinine level of 0.69 mg/dL (reference range, 0.52-1.06 mg/dL); calcium level, 9.4 mg/dL (reference range, 8.8-10.3 mg/dL); phosphate level, 4.3 mg/dL (reference range, 2.6-4.9 mg/dL); serum calcium and phosphorus product level, 38 mg^2/dL^2 (reference, <55 mg^2/dL^2); parathyroid hormone level, 24 pg/mL (reference range, 12-65 pg/mL); aspartate aminotransferase level, 31 U/L (reference range, 17-42 U/L); alanine aminotransferase level, 43 U/L (reference range, 11-50 U/L); albumin level, 2.8 g/dL (reference range, 3.5-4.8 g/dL), and international normalized ratio 2.0. Lupus anticoagulant screen was positive with negative Russell viper venom time; there was no factor V Leiden mutation; β2-glycoprotein IgG and IgM levels were less than 21 SGU; homocysteine level, 10 µmol/L (reference range, 4-14 µmol/L); antithrombin III activity, 88% (reference range, 79%-120%); and protein C activity, 101% (reference range, 76%-146%). Culture of the ulcer was negative for acid-fast bacilli. (To convert creatinine to micromoles per liter, multiply by 88.4; to convert calcium to millimoles per liter, multiply by 0.25; to convert aspartate aminotransferase and alanine aminotransferase to microkatals per liter, multiply by 0.0167; and to convert albumin to grams per liter, multiply by 10.)

A second biopsy specimen showed calcification of small- to medium-size vessels within the subcutis and fat necrosis without neovascularization (**Figure 2**A). A von Kossa stain revealed perieccrine calcium deposition (Figure 2B). Owing to the presence of calcium within vessels in the subcutis, subcutaneous fat necrosis, perieccrine calcium deposition, and lack of clinically significant neovascularization, along with progression of clinical morphologic characteristics into fixed purpura, a diagnosis of calciphylaxis was made.

Warfarin was identified as the precipitant because the patient did not have renal failure or other risk factors. Treatment with rivaroxaban, pentoxifylline, and sodium thiosulfate resulted in full recovery.

Figure 1. Clinical Presentation

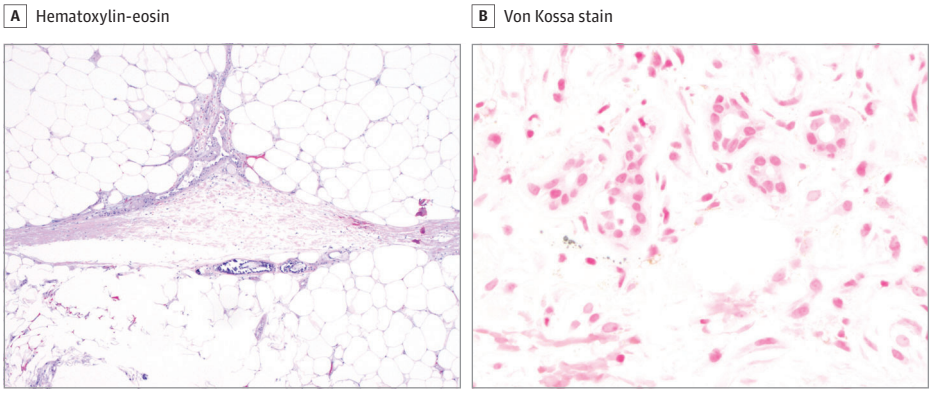


A, Tender indurated plaques with central ulceration, purpuric borders, and surrounding fixed retiform purpura. B, Ulcers resolved after 8 weeks of intravenous sodium thiosulfate treatment.

Review of the Literature

We searched MEDLINE and Ovid without language or date restrictions using the terms "calciphylaxis and warfarin," "nonuremic calciphylaxis," and "nonuremic calciphylaxis." We defined nonuremic calciphylaxis as a histopathologic diagnosis

Figure 2. Histopathologic Image of Calciphylaxis



A, A combination of calcification of small- to medium-size vessels in concert with fat necrosis with varying sized adipocytes juxtaposed to lipophages (original magnification ×100). B, A von Kossa stain highlights small foci of perieccrine calcium deposition (original magnification ×400).

of calciphylaxis without severe kidney disease (serum creatinine level >3 mg/dL, GFR<15 mL/min, acute kidney injury requiring dialysis, and renal transplantation). We found 15 cases of warfarin-associated nonuremic calciphylaxis in the literature and 3 cases from our institution.[5-9]

Patients were predominantly female (15 of 18 [83%]). Lesions were usually below the knees (12 of 18, 67%) but also on thighs, abdomen, and breasts (6 of 18 [33%]). Duration of warfarin prior to calciphylaxis onset ranged from 1 to 168 months (mean, 32 months). No cases reported elevated calcium-phosphate product, hypercoagulability, or rheumatologic disease (**Table 1** and **Table 2**).

Histopathologic analysis revealed calcification in all cases, most often in the tunica media (n = 8 [44%]) or in the vessel lumen and tunica intima (n = 7 [39%]). Other findings included ischemia and/or necrosis (n = 10 [56%]), extravascular calcification (n = 7 [39%]), endovascular fibrosis and/or hyperplasia (n = 6 [33%]), and thrombosis (n = 5 [28%]). Multiple biopsy specimens were required in 8 cases (44%) to render a definitive diagnosis.

Treatments included heparin (n = 13 patients [72%]), sodium thiosulfate (n = 9 [50%]), and hyperbaric oxygen (n = 3 patients [17%]). Three cases did not report either continuing or discontinuing warfarin; every other case reported stopping warfarin therapy. Survival to discharge was high (n = 15 patients [83%]). We did not observe recurrence after cessation of warfarin.

Discussion

Calciphylaxis was the most probable diagnosis in the case described herein because of the combination of specific histopathologic features, consistent morphologic characteristics, and exclusion of other disease (vasculitis, thrombophilia, and infection). The most compelling histopathologic evidence for calciphylaxis is a combination of vascular calcification of small- to medium-size vessels with fat necrosis and proximal vascular thrombosis. Distinguishing calciphylaxis from atherosclerotic disease with secondary vascular calcification and necrosis is challenging. Thrombosis is absent in atherosclerosis, but may also be missed in calciphylaxis owing to sampling error. A von Kossa stain may reveal perieccrine calcification, which can support the diagnosis of calciphyalxis.[20] Perieccrine calcification was present in this case, strongly supporting the diagnosis of calciphylaxis in the context of stellate ulceration and exclusion of other disease.

In this series, warfarin-associated calciphylaxis often occurred in the presence of other risk factors for vessel narrowing or thrombosis, but these factors were not sufficient to cause disease. In our case series, warfarin was the proximal inciting risk factor for calciphylaxis, and symptoms resolved after discontinuation of warfarin. Although warfarin is an anticoagulant, it increases the odds of calciphylaxis up to 10-fold.[1,3,21]

The pathogenesis of warfarin-associated calciphylaxis is incompletely understood, but distinct from both classic calciphylaxis and warfarin-induced necrosis. Evidence suggests that warfarin promotes vascular calcification by inhibiting vitamin K-dependent matrix Gla protein, a protein that prevents calcium deposition in arteries.[22] Thrombosis, the second step necessary for calciphylaxis, is counterintuitively increased by warfarin. We suspect that warfarin incites thrombosis by acting on vascular endothelial cells, which regulate the local microenvironment of procoagulant and anticoagulant factors by secreting proteins C and S in response to stress.[23] Warfarin decreases protein S secretion in cultured endothelial cells by more than 90%.[24] Thus, warfarin may inhibit normal endothelial cell responses to calcification and stress by blocking protein C and S, tipping the local balance in favor of thrombosis. This is distinct from systemic protein C and S deficiency, which typically occurs within 2 weeks and causes venous, not arterial, thrombosis.

Clinically, warfarin-associated calciphylaxis and classic calciphylaxis both present with indurated plaques with overlying retiform purpura and central necrosis. However, this study identifies key differences between the 2 diseases. Warfarin-associated calciphylaxis tends to ulcerate below the knee, while ulcerations of classic calciphylaxis are usually proximal and over fat-bearing regions.[1,4] Most important, mortality for warfarin-associated calciphylaxis in this study is 17%, much lower than the 50% to 80% mortality of classic calciphylaxis.[1,4] This difference may be confounded by absence of renal failure in our population and the distal location of ulcers.[4]

Table 1. Patient Characteristics, Treatment, and Outcome

Source	Sex/Age, y	Warfarin Duration, mo	Reason for Warfarin	Comorbidities	Cr, mg/dL	Ca-Phos Product	PTH, ng/L	Other Significant Medications	Treatment	Outcome
Huang et al,[10] 2013	M/19	1	Bilateral iliac vein stents	Chronic hypercalcemia	2.1	52	6.32	NR	Wound care, D/C warfarin	Survived
Hafiji et al,[9] 2013	M/54	9	Atrial fibrillation	DM2, CHF, bronchiectasis	WNL	WNL	WNL	Chronic doxycycline	Sodium thiosulfate (25 g, TIW, for 8 mo), maggot debridement, D/C warfarin	Survived
Spanakis et al,[11] 2013	F/86	48	DVT	Polymyalgia rheumatica	1.1	33	47	Glucocorticoid teriparatide	Zoledronic acid, D/C teriparatide, warfarin D/C then restarted	Survived
Asobie et al,[5] 2008	F/58	5	Atrial fibrillation	Chronic anemia	WNL	WNL	WNL	NR	Heparin, prednisolone, minocycline, D/C warfarin, pentoxyfylline	Survived
Banerjee et al,[6] 2010	F/63	NR	DVT	BMI, 39; DM2; HLD; CAD; HTN	1.07	32	90	NR	Enoxaparin, HBO, pentoxifylline, D/C warfarin	Survived
Kalajian et al,[12] 2009	F/58	NR	DVT	BMI, 53; HTN; hypothyroidism; endometrial carcinoma	0.4-0.8	42	63	Carboplatin and paclitaxel	Enoxaparin, cinacalcet, sevelamer, ergocalciferol, sodium thiosulfate (5 g/d for 6 mo), warfarin D/C then restarted	Survived
Hackett et al,[8] 2009	F/44	168	DVT	BMI, 52; hypothyroidism; hypoparathyroid	WNL	WNL	<20	L-thyroxine, calcium, and vitamin D	Heparin, alfacalcidol, pamidronate, sodium thiosulfate (25 g, TIW, for 7 mo), D/C warfarin	Survived
Banky et al,[7] 2002	F/68	NR	Atrial fibrillation	HTN	0.79	3	6.8	NR	Ciprofloxacin, prednisolone, LMWH, etidronate, HBO, bilateral leg amputation, D/C warfarin	Survived
Almafragi et al,[13] 2009	F/54	3	Atrial fibrillation	HLD, CAD, HTN, CHF	0.9	NR	17	NR	Antibiotics, bisphosphonates	Survived
Bosler et al,[14] 2007	F/73	NR	Atrial fibrillation	Obesity, DM2, HTN, breast and endometrial carcinoma with bony metastases	1.0-2.0	WNL	31	NR	Surgical debridement, topical silver, corticosteroids, urea	Survived
Riegert-Johnson et al,[15] 2001	F/54	3	DVT	Cholangio-carcinoma	1.6	27	2	Phenytoin, gemcitabine, cisplatin	Vitamin K, ardeparin, D/C Warfarin	Death (sepsis)
Erdel et al,[16] 2014	F/47	4	Atrial fibrillation	BMI, 37; chronic hypopara-thyroidism	WNL	44	NR	Calcitriol, calcium supplements	Sodium thiosulfate (25g IV TIW)	Death (sepsis)
Ong and Coulson,[17] 2011	F/79	>24	Atrial fibrillation	HTN	WNL	WNL	WNL	NR	Sodium thiosulfate (25 g, TIW for 8 weeks), pamidronate, D/C warfarin	Survived
Dominguez and Goldman,[18] 2014	F/66	>24	Pulmonary emboli	Obesity, osteoporosis, RA	WNL	WNL	WNL	Teriparatide, prednisone, leflunomide	Sodium thiosulfate (dose not reported), D/C warfarin and teriparatide	Death (respiratory depression)
Wanat et al,[19] 2014	F/60	84	Artificial aortic valve	BMI, 32.3; DM2; HLD; CHF; HTN	WNL	WNL	WNL	NR	Dabigatran, sevelamer, HBO, alendronate, D/C warfarin	Survived
Present report, patient 1	F/60s	24	Atrial fibrillation	BMI, 38; DM2; HLD; HTN; RA	0.69	38	24	Methotrexate, colchicine, prednisone	Sodium thiosulfate (25g TIW for 8 wk), D/C warfarin, rivaroxaban, pentoxyfylline	Survived

(continued)

Warfarin-induced skin necrosis differs from warfarin-associated calciphylaxis in clinical presentation and pathogenesis. Warfarin-induced skin necrosis presents with hemorrhagic bullae with surrounding retiform purpura 3 to 10

Table 1. Patient Characteristics, Treatment, and Outcome (continued)

Source	Sex/Age, y	Warfarin Duration, mo	Reason for Warfarin	Comorbidities	Cr, mg/dL	Ca-Phos Product	PTH, ng/L	Other Significant Medications	Treatment	Outcome
Present report, patient 2	F/80s	36	Atrial fibrillation	BMI, 28; DM2; HTN; Polymyalgia rheumatica	0.53	31	35	Colchicine	Sodium thiosulfate (12.5g TIW for 6 weeks), rivaroxaban, D/C warfarin	Survived
Present report, patient 3	M/40s	3.5	Atrial fibrillation	BMI, 34; DM2; HLD; HTN; CHF	1.11	37.38	52.2	NR	Sodium thiosulfate (25 g, IV TIW), pentoxifylline, dabigatran, D/C warfarin	Survived

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CAD, coronary artery disease; CHF, congestive heart failure; D/C, discontinued; DM2, diabetes mellitus type 2; DVT, deep vein thrombosis; HBO, hyperbaric oxygen; HLD, hyperlipidemia; HTN, hypertension; IV, intravenous; LMWH, low molecular weight heparin; NR, not reported; RA, rheumatoid arthritis; TIW, 3 times a week; WNL, within normal limits.

days after warfarin initiation, whereas warfarin-associated calciphylaxis presented on average after 32 months as indurated retiform purpuric plaques with central necrosis favoring the lower extremities. Warfarin-induced skin necrosis arises from immediate hypercoagulability from decreased systemic protein C and S, whereas warfarin-associated calciphylaxis probably involves chronic vascular calcification and local inhibition of protein C and S with normal systemic levels.

These distinctions inform clinical management of warfarin-associated calciphylaxis. Clinicians should be alert to necrotic skin lesions well past the 10-day interval typical of warfarin-induced skin necrosis. Warfarin should be stopped, but protein C replacement is not beneficial because there is no systemic deficiency in protein C. Thrombolytics or anticoagulants can be used to reestablish perfusion. Sodium thiosulfate and/or bisphosphonates seem to benefit patients with nonuremic calciphylaxis, arguing that these therapies do more than alter the calcium-phosphate product.[25] Sodium thiosulfate, for example, has antioxidant properties that aid wound healing.[25] Vitamin K supplementation could theoretically counteract warfarin induced arteriolar calcification. The VitaVasK trial (NCT01742273), an evaluation of vitamin K for reducing vascular calcification, may provide evidence for vitamin K treatment in calciphylaxis.

Table 2. Laboratory Evidence of Hypercoagulability and Autoantibodies

Assay	Result, No./Total No.[a]	Normal, %
Antiphospholipid antibody	11/13	85
Protein C and S activity	11/11	100
Factor V Leiden mutation	7/7	100
Cryoglobulins	6/6	100
Serum protein electrophoresis	4/4	100
Antinuclear antibody	7/10	70
Antineutrophil cytoplasmic antibody	5/5	100
Rheumatoid factor	5/5	100

[a] Numerator represents the number of cases reporting a normal result, denominator represents number of cases in which test was performed.

Conclusions

Patients with warfarin-associated calciphylaxis are a distinct subgroup of patients with calciphylaxis. In particular, patients with warfarin-associated calciphylaxis have no calcium imbalance and have a favorable prognosis compared with those with classic calciphylaxis. Warfarin may cause both calcification of arteries and paradoxical thrombosis through local action on vascular endothelium. Better understanding the pathogenesis of calciphylaxis may lead to more specific and effective therapies.

ARTICLE INFORMATION

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Author Contributions: Drs Yu and Fox had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Yu, Bhutani, Rosenblum, Fox.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Yu, Pincus, Mauro, Rosenblum.
Critical revision of the manuscript for important intellectual content: Yu, Bhutani, Kornik, Pincus, Rosenblum, Fox.
Statistical analysis: Yu.
Administrative, technical, or material support: Rosenblum.
Study supervision: Fox.

Conflict of Interest Disclosures: None reported.

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NOTABLE NOTES

Harvey Cushing, MD—A Neurosurgeon's Contributions to Cutaneous Pathology

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Harvey Williams Cushing, MD, was born on April 8, 1869, in Cleveland, Ohio, as the youngest of 10 siblings. He attended Cleveland Manual Training School as a child, where he learned carpentry, metal work, and machinery skills that would later help him develop his technical abilities as a surgeon. Cushing came from a family with 3 generations of physicians, and he began his medical career at Harvard Medical School in 1891. Cushing trained at numerous institutions, including Massachusetts General Hospital, where he trained under John Wheelock Elliot, MD, who directed his attention to surgery of the brain. Through these experiences Cushing helped establish neurological surgery over the length of his career as a viable medical specialty and earned the title of "the father of modern neurosurgery." He faced adversity from critics who did not believe in the viability of brain surgery; however, he found constant encouragement from William Osler, MD (1849-1919), whose mentorship helped him push the boundaries of surgical innovation.[1]

During his training at Johns Hopkins Hospital in 1910, Cushing encountered a 23-year-old woman who presented with an enlarged abdomen, mimicking that of a full-term pregnancy; she also had supraclavicular fat pads, a rounded face, and abnormal hair growth on the face, hips, and back. Cushing's case report stated that her "skin during the past few years has become rough and dry and has a blue and dusky appearance. The body and extremities show an especial degree of cyanosis. There are a number of large subcutaneous ecchymoses over the lower extremities. The lineae atrophicae over the abdomen are of a deep brownish-purple color. There is considerable pigmentation, particularly of eyelids, groins, pubes, and areolae."[2] Although prior accounts had reported similar symptoms of adrenal etiology, Cushing was the first to connect the symptomatology to a pituitary basophil adenoma, grouping the findings as "polyglandular syndrome."[2] Suprasellar surgical techniques were still primitive, but Cushing performed a decompressive craniectomy with some symptomatic relief 1 month after the operation.[2] His meticulous characterization brought new connections between endocrine pathology and cutaneous manifestations.

Outside of medicine, one of Cushing's long-standing hobbies was collecting and writing books. His book collection included a broad range of subjects, including books on herbalism, astronomy, general surgery, and anesthesia.[1] He eventually donated his book collection, including a Brain Tumor Registry describing his interactions with his patients, to his alma mater, Yale University. In 1940, the university built the Harvey Cushing/John Hay Whitney Medical Library to honor him. In appreciation for his mentor, Cushing wrote a Pulitzer Prize–winning biography of Dr Osler called *The Life of Sir William Osler*.[3] Cushing died at the age of 70 years on October 7, 1939, as the result of a posterior coronary myocardial infarction.[1]

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