CASE REPORT

Case Report: Medial prefrontal syndrome in a coup de sabre scleroderma carrier

[version 1; peer review: 1 approved with reservations, 1 not approved]

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Abstract

Introduction: Linear scleroderma *en coup de sabre* is a subtype of scleroderma hallmarked by cutaneous and extracutaneous manifestations in which neurological symptoms can be a predominant feature of this condition.

Case presentation: We report a case of a previously healthy 47-year-old male who developed neuropsychiatric symptoms and right-sided cephalalgia for two months. Clinical examination revealed a right frontoparietal cutaneous lesion and neurological findings suggesting a medial prefrontal syndrome. The neuroimaging evaluation identified scalp and bone thinning adjacent to the skin lesion and cortical-subcortical white matter hyperintensity due to vasogenic oedema at the right frontal and parietal region. A biopsy from the affected area revealed reactive gliosis.

Conclusion: To our knowledge, this is the first linear scleroderma *en coup de sabre* report associated with a neurological involvement typical of a medial prefrontal syndrome. This case highlights the importance of clinical acuity in recognising atypical phenotypes within the spectrum of this uncommon disease.

Keywords

Localized Scleroderma, Linear Scleroderma en coup de sabre, Morphea, Neurologic involvement, Neurologic manifestations, prefrontal syndrome

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Introduction

Scleroderma is an immune-mediated and chronic connective tissue disease typified by a pathogenic triad encompassing vasculopathy due to endothelial dysfunction, dysregulation of innate and adaptive immunity, and progressive tissue fibrosis affecting the skin and multiple internal organs.[1] This entity has traditionally been classified into systemic and localised forms.[2] Systemic scleroderma, or systemic sclerosis (SS), can manifest at any age, mainly in adults. Like most autoimmune disorders, prevalence is higher in females.[3] The SS epidemiological behaviour is notably variable due to its rarity, the broad clinical symptoms spectrum, the changing diagnostic criteria, and evolving classifications. These features complicate a comparative analysis plausibility across studies and an accurate prevalence trends estimation.[4] In this vein, a recent meta-analysis encompassing 82 studies[5] revealed that 83.9% of the world's countries had not reported systemic scleroderma epidemiological data. This study projected a global incidence of 8.64 affected individuals per 100,000 persons annually (range: 1.78 to 23.57). The prevalence was calculated as 18.87 per 100,000 (range: 1.55–25.28), approximating 1.47 million (range: 0.12–1.97 million) affected individuals globally. Incidence and prevalence were higher in females, adults, and high-income countries.[5]

Localised scleroderma (LS), or morphea, is delineated by skin lesions and involvement of underlying tissues (e.g., fascia, subcutaneous cellular tissue). Based on the extent and depth of fibrotic changes, LS is classified into limited, generalised, deep, mixed, and linear subtypes.[6] LS incidence ranges from 0.3 to 3 per 100,000 individuals/year, affecting children and adults equally.[7] Although it is primarily seen as a skin-limited disease, certain subtypes exhibit extracutaneous manifestations, including musculoskeletal (myositis, fasciitis, arthritis), central nervous system (headache, migraine, seizures, epilepsy), and ocular (uveitis) involvements.[8] LS encompasses forms leading to progressive facial hemiatrophy (Parry-Romberg Syndrome) and those affecting facial and cranial regions without facial hemiatrophy (linear scleroderma *en coup de sabre,* LSCS), the latter initially described by Addison in 1854.[6] In this sense, band-like sclerotic lesions located on the face and usually extended to the head, skin atrophy groove formation, underlying tissue changes, localised alopecia, and occasional changes in skin pigmentation are the typical presentation of LSCS. Though rare, neurological involvement has been described as epileptic seizures, cephalalgia, focal neurological deficits, and neuropsychiatric symptoms.[9] Given the rarity of LSCS and the uncommon coexistence of neurological manifestations beyond epileptic seizures, we detail a case of LSCS associated with clinical neurological features compatible with a medial prefrontal syndrome.

Case presentation

A 47-year-old professional truck driver, right-handed Hispanic male consulted our neurology department because of a 2-month history of behavioural changes. As reported by his spouse, these changes included apathy, anhedonia, abulia, decreased sociability, reduced spontaneous speech progressing towards mutism, irritability, and emotional lability. In addition, the patient refers to a right-pulsatile hemicranial headache with moderate intensity. There was no significant personal or familial past medical history. Initial physical examination revealed a sclerotic, depressed band with skin atrophy and alopecia extending from the forehead to the right parietal region. After inquiring with family members, this lesion progressed for over two years (Figure 1). Neurological examination demonstrated spatial disorientation, reduced spontaneous speech, decreased spontaneous motor activity, and reduced task-directed behaviours. Dysphoria was evident, but there were no speech or mnesic function disturbances. On the Montreal Cognitive Assessment (MoCA) scale, he scored 15/30, indicating impairments in executive function, cognitive flexibility, and mathematical reasoning. Cranial nerve examination, motor evaluation, sensory assessment, coordination, and gait were all within normal limits. The rest of the physical examination was unremarkable.

Laboratory tests showed elevated erythrocyte sedimentation rate (ESR): 24 mm/h (reference range: 0.0–15.0 mm/h), raised C-reactive protein (CRP): 32.50 mg/l (reference range: 0.00–10.00 mg/l), and decreased vitamin B12 levels: 140.8 pg/ml (reference range: 174.0–878.0 pg/ml). Blood analysis, kidney and liver function, ionogram, glucose levels, coagulation tests, veneral disease research laboratory (VDRL), ELISA HIV, tumor markers (prostate antigen, CA 19-9, alpha-fetoprotein, carcinoembryonic antigen), vitamin B1, folic acid, and autoimmune profile (anti-nuclear antibodies (ANA), anti-double stranded DNA antibodies (Anti-dsDNA), anti–Sjögren's-syndrome-related antigen A antibodies (AntiRo/SSA), anti–Sjögren's-syndrome-related antigen B antibodies (AntiLA/SSB), anti-Smith antibodies (Anti-SM), anti-ribonucleoprotein antibodies (Anti-RNP), antiphospholipid IgG and IgM, serum complement C3, C4, lupus russell viper anticoagulant venom test) were all within normal ranges.

Cerebrospinal fluid (CSF) macroscopic analysis showed a clear, transparent pH of 8 liquid. The cellular count was 0.003 cells/ul (leukocytes: 0–2 xc, erythrocytes: 0–3 xc), with 20% in polymorphonuclear cells, 80% in mononuclear cells and no bacteria observed at the microscope observation. CSF chemical analysis exhibited a glucose concentration of 74 mg/dl, 21.5 mg/dl proteins, and negative results for India ink and gram stains. Moreover, potassium hydroxide (KOH) test and culture stains showed no evidence of microorganisms.

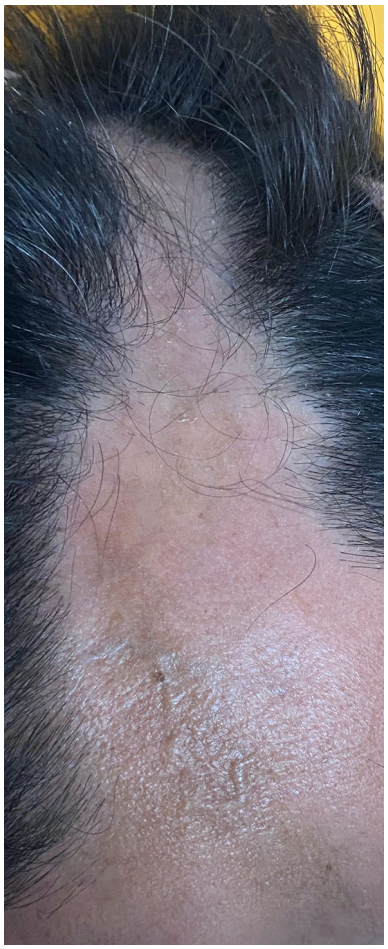

Figure 1. Fibrotic, firm, and depressed band extending from the right superciliary arch to 4 cm above the hairline, covered by smooth and shiny nacreous-colored skin, associated with an alopecia band in the affected area.

Non-contrast and contrast-enhanced brain magnetic resonance imaging (MRI) revealed right frontal epicranial tissues and diploë thinning, a subcortical and deep white matter increased T2 signal, suggestive of vasogenic edema at the right cingulate gyrus, superior frontal gyrus, supramarginal gyrus and superior temporal gyrus. Underlying the high T2 area of vasogenic edema, there was a focal lesion which exhibited a low signal on the echo gradient sequence due to calcification at the right superior frontal gyrus with slight gadolinium lesional enhancement (Figure 2).

The patient was hospitalised for further evaluation. General measures were implemented, including gastroprotection, thromboprophylaxis, and analgesia for the headache, and he was started on antiepileptic medication Valproic Acid 500 mg every 8 hours for seizure prevention and Sertraline 50 mg daily for mood management. Given the non-specific findings on MRI and the differential diagnosis considering a neoplastic lesion, it was decided to further the diagnostic workup with an electroencephalogram, spectroscopy analysis and scheduled for a stereotactic biopsy.

Lesions spectroscopy of the described revealed no elevated choline peaks and preserved n-acetyl-aspartate levels. On the eighth day of admission, the patient underwent a stereotactic biopsy. Post-procedure, the patient was transferred to an intermediate care unit for neurological monitoring and initiated on corticosteroid therapy with Dexamethasone 4 mg IV every 8 hours.

A follow-up non-contrast MRI of the brain, taken 24 hours post-surgery, showed minimal bleeding at the biopsy site and no evidence of vasogenic oedema progression compared to the initial neuroimaging assessment. Clinical examination remains unchanged from the evaluation at admission.

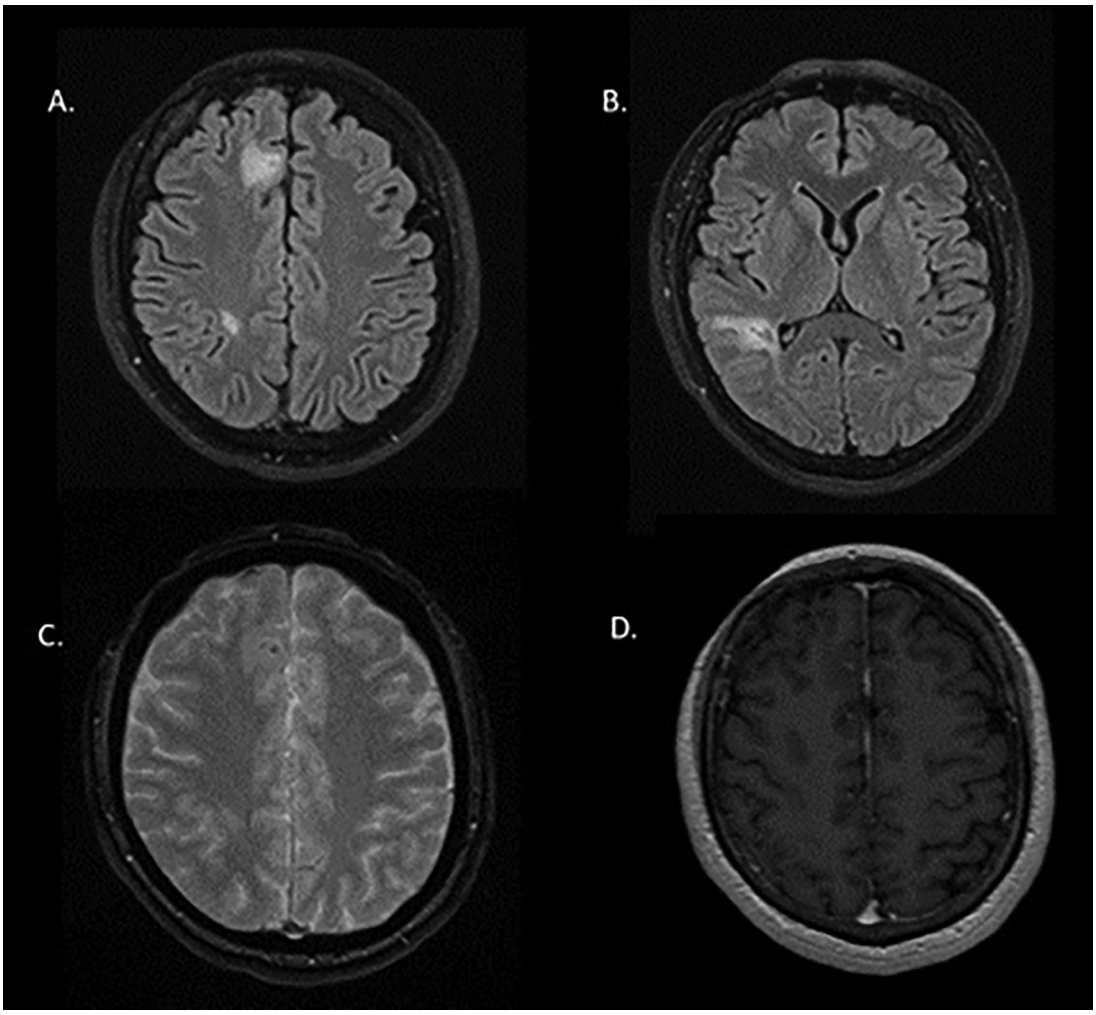

Figure 2. (A) Axial section of a brain magnetic resonance imaging in fluid attenuated inversion recovery sequence showing an area of high T2 relative to the brain parenchyma, located in the right frontal and parietal regions due to vasogenic edema. An eccentric hypointensity is evident, corresponding to the lesion area. (B) Vasogenic edema is observed with a central hypointense lesion adjacent to the temporal horn of the right lateral ventricle. (C) The lesion shows low signal in the Gradient Echo sequence and (D) homogeneous enhancement in the T1-weighted sequence following gadolinium administration.

Table 1. Case reports of neurologic manifestations in patients with linear scleroderma en coup de sabre.

Study Type	Neurologic Manifestation	Number of Case Reports	Ref.
Case reports	Seizure	9	17,18,19,20,21,22,23,17,24
	Focal Neurologic Deficit	2	23,25
	Cranial Nerve Involvement	5	17,26,1,26,27
	Headache	4	20,22,28,29

Lesional stereotactic biopsy showed normal-looking neurons, reactive gliosis areas, acute and chronic inflammatory infiltrates, and no evidence of microorganisms, granulomas, or malignancy at cerebral parenchyma. Immunohistochemical markers showed positivity for glial fibrillary protein (GFAP) and S-100 in the reactive astrocytes.

On the eleventh day post-admission, the patient experienced a sudden episode of retrosternal pain, dyspnea, desaturation, hypotension, and bradycardia, culminating in cardiac arrest. Despite immediately initiating basic and advanced cardiopulmonary resuscitation measures, the patient could not be resuscitated and was pronounced deceased.

Table 2. Case series and systematic reviews of neurologic manifestations in patients with linear scleroderma en coup de sabre.

Study Type	Neurologic Manifestation	Frequency	Ref.
Case series	Headache	8/26	30
	Seizure	6/26	
	Focal Neurologic Deficit	2/26	
	Cranial Nerve Involvement	3/26	
	Seizure	4/9	31
	Headache	3/5	9
	Seizure	2/5	
	Focal Neurologic Deficit	3/5	
	Headache	5/12	32
	Seizure	3/12	
	Focal Neurologic Deficit	4/12	
	Neuropsychiatric Symptons	1/12	
Systematic review	Epilepsy	140	33
	Headache	19/92	16*
	Seizure	42/92	
	Focal Neurologic Deficit	15/92	
	Neuropsychiatric Symptons	4/92	
	Cranial Nerve Involvement	8/92	

*This systematic review included patients with Parry-Romberg Syndrome.

Discussion

LS, or morphea, is a rare immunoinflammatory disorder of the connective tissue affecting both adults and children,[2] with a clear sex predominance in women with a 2–4:1 ratio.[7] LS incidence ranges between 0.3 and 3 cases per 100,000 individuals annually,[4] and although it occurs across all ethnicities, the White population exhibits the highest prevalence, followed by Latin American and other Hispanic-related groups.[7]

LSCS, also known as frontoparietal linear morphea or *en coup de sabre scleroderma*, is a rare variant of LS affecting the skin and bone in the frontoparietal region.[10] LSCS is a very rare condition; most of the scientific literature indicates that it only accounts for 2–4% of linear scleroderma cases in adults, contrasting to the fourth-fold increase in LSCS prevalence in children with 3–17%.[11] Based on an extensive and systematic literature review in Scopus, Web of Science, PubMed and Google Scholar, fewer than 100 case reports have been published on adult-onset LSCS,[12–14] with only one case reported in Colombia.[15] In Table 1 and Table 2, we present the case reports, cases series, and systematics reviews of patients with neurological manifestations identified during our literature search. Indeed, after this extensive search, we did not identify any studies specifically detailing the mediofrontal syndrome as a neuropsychiatric manifestation of neurological involvement in LSCS; thus, to our knowledge, this is the first report related to this association. In this regard, the accumulation of descriptive evidence from clinical case reports has enlightened previously considered an atypical manifestation, nervous system involvement in scleroderma is now increasingly recognised. Headache and seizures are the most frequently reported neurological manifestations in LSCS.[16]

The underlying pathophysiology of linear scleroderma remains only partially understood. It is believed to involve various factors, including genetics, environmental influences (such as trauma and infections), and disruptions in the immune system, primarily characterised by increased cytokine production. Based on current evidence, the pathophysiological process of morphea can be divided into three distinct phases: 1. early inflammatory, 2. sclerotic/fibrotic, and 3. late atrophic.[34] In LSCS, both clinical and histopathological findings suggest a complex interaction between the vasculature and the immune system. Like SS, CD4 T lymphocytes appear to be associated with the fibrotic changes in these lesions. Initially, TH1 and TH17 inflammatory pathways predominate and later, fibrotic changes are believed to arise due to a shift in these inflammatory pathways, with a TH2 response dominance.[35] Eventually, atrophy occurs, characterised by epidermal thickness, blood vessels, and inflammatory cell loss.[34]

LSCS typically presents as a solitary, linear, fibrous plaque that affects the skin and muscle, depressing the underlying bone and resembling the strike of a sabre – hence its name.[10] Many authors consider extracutaneous manifestations of localised scleroderma extremely rare, with only approximately 20% of patients developing them. Among these manifestations, arthritis, uveitis, and epileptic seizures are predominantly observed, with neurological manifestations being the most frequent among them.[22]

Our patient exhibited atypical features and manifestations. One was a medial frontal syndrome as an initial clinical feature. According to the systematic review published by Amaral *et al.,*[16] the most common neurological manifestations in linear scleroderma are epileptic seizures, affecting 41% of patients, followed by headaches in 18.8%. Only 1–3% exhibited cognitive decline and behavioural changes.

Additionally, another uncommon feature of our patient was his male gender. In the report by Taniguchi *et al.,*[36] out of 16 cases of LSCS, only three were male, and none exhibited neurological manifestations. Among the 13 females, only five presented neurological manifestations, including headaches and abnormal findings in the electroencephalogram, akin to the observations reported by Amaral *et al.*[16] None displayed behavioural or cognitive alterations.

Regarding complementary studies, abnormal neuroimaging findings exist in approximately 84% of patients. In a case report and literature review by Kister *et al.*, only 11% of patients had normal brain MRIs. The remainder exhibited at least one T2 hyperintense lesion, primarily in the subcortical white matter and the *corpus callosum*, basal ganglia, and brainstem. These lesions were ipsilateral to the skin lesion in 88% of the patients. The predominance of these ipsilateral lesions to the skin manifestation suggests a potential pathogenic correlation between cerebral damage and the dermatological lesion, though the exact mechanism remains a topic of debate and investigation.[22]

On the other hand, it is relevant to consider that while a significant proportion of patients may exhibit abnormal brain MRI, not all of them experience overt clinical symptoms. This phenomenon underscores the need for regular neurological and radiological monitoring, allowing for early patient intervention in those who might develop complications. Some of these findings were identified during our patient evaluation, notably in subcortical and deep white matter hyperintensities ipsilateral to the skin lesion.

Regarding treatment, management guidelines recommend systemic therapy for localised scleroderma. Methotrexate, either as monotherapy or combined with corticosteroids, is suggested as a first-line treatment.[37,38] Additionally, positive outcomes with mycophenolate and tocilizumab have been reported in other publications.[39] Our patient received corticosteroid treatment consistent with descriptions in other case reports and as recommended in clinical practice guidelines. However, we could not monitor the treatment response and clinical progress due to the patient's demise from a non-neurological complication. Nevertheless, the follow-up imaging did not reveal the progression of the lesions noted in subsequent MRI scans.

Case report consent

Written informed consent for publication of their clinical details and clinical images was obtained from the patient's relative.

Data availability

All data underlying the results are available as part of the article, and no additional source data are required.

References

1. Denton CP, Khanna D: **Systemic sclerosis.** *Lancet.* 2017 Oct 7; **390** (10103): 1685–1699. Epub 2017 Apr 13.
PubMed Abstract | Publisher Full Text

2. Rongioletti F, Ferreli C, Atzori L, *et al.*: **Scleroderma with an update about clinico-pathological correlation.** *G. Ital. Dermatol. Venereol.* 2018 Apr; **153**(2): 208–215. Epub 2018 Jan 24.
PubMed Abstract | Publisher Full Text

3. Medsger TA Jr, Masi AT: **Epidemiology of systemic sclerosis (scleroderma).** *Ann. Intern. Med.* 1971 May; **74**(5): 714–721.
PubMed Abstract | Publisher Full Text

4. Zhong L, Pope M, Shen Y, *et al.*: **Prevalence and incidence of systemic sclerosis: A systematic review and meta-analysis.** *Int. J. Rheum. Dis.* 2019 Dec; **22**(12): 2096–2107. Epub 2019 Oct 16.
PubMed Abstract | Publisher Full Text

5. Tian J, Kang S, Zhang D, *et al.*: **Global, regional, and national incidence and prevalence of systemic sclerosis.** *Clin. Immunol.* 2023 Mar; **248**: 109267. Epub 2023 Feb 15.
PubMed Abstract | Publisher Full Text

6. Careta MF, Romiti R: **Localized scleroderma: clinical spectrum and therapeutic update.** *An. Bras. Dermatol.* 2015 Jan-Feb; **90**(1): 62–73.
PubMed Abstract | Publisher Full Text | Free Full Text

7. Peterson LS, Nelson AM, Su WP, *et al.*: **The epidemiology of morphea (localized scleroderma) in Olmsted County 1960-1993.**

J. Rheumatol. 1997 Jan; **24**(1): 73–80.
PubMed Abstract

8. Snarskaya ES, Vasileva KD: **Localized scleroderma: actual insights and new biomarkers.** *Int. J. Dermatol.* 2022 Jun; **61**(6): 667–674. Epub 2021 Aug 4.
PubMed Abstract | Publisher Full Text

9. Pinho J, Rocha J, Sousa F, *et al.*: **Localized scleroderma en coup de sabre in the Neurology Clinic.** *Mult. Scler. Relat. Disord.* 2016 Jul; **8**: 96–98. Epub 2016 May 20.
PubMed Abstract | Publisher Full Text

10. Pierre-Louis M, Sperling LC, Wilke MS, *et al.*: **Distinctive histopathologic findings in linear morphea (en coup de sabre) alopecia.** *J. Cutan. Pathol.* 2013 Jun; **40**(6): 580–584. Epub 2013 Mar 18.
PubMed Abstract | Publisher Full Text

11. Lis-Święty A, Skrzypek-Salamon A, Ranosz-Janicka I, *et al.*: **Localized scleroderma: clinical and epidemiological features with emphasis on adulthood- versus childhood-onset disease differences.** *J. Eur. Acad. Dermatol. Venereol.* 2017 Oct; **31**(10): 1595–1603. Epub 2017 Apr 3.
PubMed Abstract | Publisher Full Text

12. Mertens JS, Seyger MM, Kievit W, *et al.*: **Disease recurrence in localized scleroderma: a retrospective analysis of 344 patients with paediatric- or adult-onset disease.** *Br. J. Dermatol.* 2015 Mar; **172**(3): 722–728. Epub 2015 Feb 8.
PubMed Abstract | Publisher Full Text

13. Mazori DR, Wright NA, Patel M, *et al.*: **Characteristics and treatment of adult-onset linear morphea: A retrospective cohort study of 61 patients at 3 tertiary care centers.** *J. Am. Acad. Dermatol.* 2016 Mar; **74**(3): 577–579.
PubMed Abstract | Publisher Full Text

14. Yamasaki R, Yonekawa T, Inamizu S, *et al.*: **A case of overlapping adult-onset linear scleroderma and Parry-Romberg syndrome presenting with widespread ipsilateral neurogenic involvement.** *Neuropathology.* 2020 Feb; **40**(1): 109–115. Epub 2019 Nov 27.
PubMed Abstract | Publisher Full Text

15. García Martos Á, González Gómez FJ, Terrancle JI: **Stroke-mimic and scleroderma in "coup de sabre": Case report.** *Rev Colomb Reumatol Engl Ed.* 2021; **28**(4): 306–308.
Publisher Full Text

16. Amaral TN, Peres FA, Lapa AT, *et al.*: **Neurologic involvement in scleroderma: a systematic review.** *Semin. Arthritis Rheum.* 2013 Dec; **43**(3): 335–347. Epub 2013 Jul 1.
PubMed Abstract | Publisher Full Text

17. Gambichler T, Kreuter A, Hoffmann K, *et al.*: **Bilateral linear scleroderma "en coup de sabre" associated with facial atrophy and neurological complications.** *BMC Dermatol.* 2001; **1**: 9. Epub 2001 Dec 4.
PubMed Abstract | Publisher Full Text | Free Full Text

18. Sarria-Estrada S, Toledo M, Santamarina E, *et al.*: **Esclerosis mesial temporal en un caso de esclerodermia lineal en coup de sabre.** *Rev. Neurol.* 2011; **53**(05): 316.
Publisher Full Text

19. Chung MH, Sum J, Morrell MJ, *et al.*: **Intracerebral involvement in scleroderma en coup de sabre: report of a case with neuropathologic findings.** *Ann. Neurol.* 1995 May; **37**(5): 679–681.
PubMed Abstract | Publisher Full Text

20. Magro CM, Halteh P, Olson LC, *et al.*: **Linear scleroderma "en coup de sabre" with extensive brain involvement-Clinicopathologic correlations and response to anti-Interleukin-6 therapy.** *Orphanet J. Rare Dis.* 2019 May 16; **14**(1): 110.
PubMed Abstract | Publisher Full Text | Free Full Text

21. Nguyen K, Atty C, Ree A: **Linear scleroderma en coup de sabre presenting with seizures.** *Radiol Case Rep.* 2020 Sep 3; **15**(11): 2164–2170.
PubMed Abstract | Publisher Full Text | Free Full Text

22. Kister I, Inglese M, Laxer RM, *et al.*: **Neurologic manifestations of localized scleroderma: a case report and literature review.** *Neurology.* 2008 Nov 4; **71**(19): 1538–1545.
PubMed Abstract | Publisher Full Text

23. Stone J, Franks AJ, Guthrie JA, *et al.*: **Scleroderma "en coup de sabre": pathological evidence of intracerebral inflammation.** *J. Neurol. Neurosurg. Psychiatry.* 2001 Mar; **70**(3): 382–385.
PubMed Abstract | Publisher Full Text | Free Full Text

24. Takahashi T, Asano Y, Oka T, *et al.*: **Scleroderma en coup de sabre with recurrent episodes of brain hemorrhage.** *J. Dermatol.* 2016 Feb; **43**(2): 203–206. Epub 2015 Jul 15.
PubMed Abstract | Publisher Full Text

25. Corbally CM, Breckenridge A, Jampana R: **Imaging and clinical findings in a case of linear scleroderma en coup de sabre.** *BJR Case Rep.* 2016 Nov 2; **2**(4): 20150203.
PubMed Abstract | Publisher Full Text | Free Full Text

26. Miura S, Someya M, Toyama S, *et al.*: **A case of scleroderma en coup de sabre with ipsilateral hearing loss and aphakia.** *Eur. J. Dermatol.* 2019 Aug 1; **29**(4): 423–425.
PubMed Abstract | Publisher Full Text

27. Hock LE, Kontzialis M, Szewka AJ: **Linear scleroderma en coup de sabre presenting with positional diplopia and enophthalmos.** *Neurology.* 2016 Oct 18; **87**(16): 1741–1742.
PubMed Abstract | Publisher Full Text

28. Rimoin L, Arbiser J: **Improvement of "En Coup de Sabre" Morphea and Associated Headaches With Botulinum Toxin Injections.** *Dermatol. Surg.* 2016 Oct; **42**(10): 1216–1219.
PubMed Abstract | Publisher Full Text

29. Infante-Valenzuela A, Camara-Lemarroy CR, Delgado-Garcia G, *et al.*: **Steroid-responsive headache in scleroderma en coup de sabre.** *Acta Neurol. Belg.* 2017 Mar; **117**(1): 405–407. Epub 2016 Jul 18.
PubMed Abstract | Publisher Full Text

30. Doolittle DA, Lehman VT, Schwartz KM, *et al.*: **CNS imaging findings associated with Parry-Romberg syndrome and en coup de sabre: correlation to dermatologic and neurologic abnormalities.** *Neuroradiology.* 2015 Jan; **57**(1): 21–34. Epub 2014 Oct 11.
PubMed Abstract | Publisher Full Text

31. Appenzeller S, Montenegro MA, Dertkigil SS, *et al.*: **Neuroimaging findings in scleroderma en coup de sabre.** *Neurology.* 2004 May 11; **62**(9): 1585–1589.
PubMed Abstract | Publisher Full Text

32. Lis-Święty A, Brzeziń ska-Wcisło L, Arasiewicz H: **Neurological abnormalities in localized scleroderma of the face and head: a case series study for evaluation of imaging findings and clinical course.** *Int. J. Neurosci.* 2017 Sep; **127**(9): 835–839. Epub 2016 Oct 26.
PubMed Abstract | Publisher Full Text

33. Hixon AM, Christensen E, Hamilton R, *et al.*: **Epilepsy in Parry-Romberg syndrome and linear scleroderma en coup de sabre: Case series and systematic review including 140 patients.** *Epilepsy Behav.* 2021 Aug; **121**(Pt A): 108068. Epub 2021 May 28.
PubMed Abstract | Publisher Full Text

34. Papara C, De Luca DA, Bieber K, *et al.*: **Morphea: The 2023 update.** *Front Med (Lausanne).* 2023 Feb 13; **10**: 1108623.
PubMed Abstract | Publisher Full Text | Free Full Text

35. Kurzinski K, Torok KS: **Cytokine profiles in localized scleroderma and relationship to clinical features.** *Cytokine.* 2011 Aug; **55**(2): 157–164. Epub 2011 May 4.
PubMed Abstract | Publisher Full Text | Free Full Text

36. Taniguchi T, Asano Y, Tamaki Z, *et al.*: **Histological features of localized scleroderma 'en coup de sabre': a study of 16 cases.** *J. Eur. Acad. Dermatol. Venereol.* 2014 Dec; **28**(12): 1805–1810. Epub 2013 Oct 10.
PubMed Abstract | Publisher Full Text

37. Asano Y, Fujimoto M, Ishikawa O, *et al.*: **Diagnostic criteria, severity classification and guidelines of localized scleroderma.** *J. Dermatol.* 2018 Jul; **45**(7): 755–780. Epub 2018 Apr 23.
PubMed Abstract | Publisher Full Text

38. Knobler R, Moinzadeh P, Hunzelmann N, *et al.*: **European Dermatology Forum S1-guideline on the diagnosis and treatment of sclerosing diseases of the skin, Part 1: localized scleroderma, systemic sclerosis and overlap syndromes.** *J. Eur. Acad. Dermatol. Venereol.* 2017 Sep; **31**(9): 1401–1424. Epub 2017 Aug 9.
PubMed Abstract | Publisher Full Text

39. Mertens JS, Marsman D, van de Kerkhof PC, *et al.*: **Use of Mycophenolate Mofetil in Patients with Severe Localized Scleroderma Resistant or Intolerant to Methotrexate.** *Acta Derm. Venereol.* 2016 May; **96**(4): 510–513.
PubMed Abstract | Publisher Full Text

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This care report attempts to add to the literature in providing description of a novel CNS manifestation of craniofacial scleroderma. The authors present a single adult male with significant behavioral alterations, who is concurrently noted to have skin lesions consistent with craniofacial subset of localized scleroderma (*encoup de sabre* phenotype). Cognitive, laboratory, and imaging investigations identify significant cognitive difficulties and a markedly abnormal brain MRI. Although the patient unexpectedly expired in the hospital, the authors note that this was likely unrelated to his initial presentation.

Unfortunately, multiple portions of the case presentation lack sufficient detail to directly conclude that the reported symptoms were related to the purported diagnosis. In addition, there are multiple content issues that undermine confidence in the report and should be further addressed by the authors.

Case History and Details

- Elevated inflammatory markers are very uncommon in localized scleroderma, so clarification on why present in this patient, as well as additional laboratory trends would be appreciated.
- Vitamin B12 level was noted to be low, but unclear why this was not addressed in the discussion.
- Authors note EEG was obtained, but no report of results is provided; this needs to be addressed
- Lab results refer to “lupus russell anticoagulant venom test”; this terminology is incorrect and should be either “dilute Russell viper venom time” or “Russell viper venom time”.

Background and Discussion

- Authors assert that “medial frontal syndrome was initial clinical feature”, though they report that his lesion had been present for at least two years in the case presentation.
- In the discussion, reference 4 is cited as a source for localized scleroderma incidence but that reference refers to systemic sclerosis incidence.
- Extracutaneous manifestations occurring with incidence of 20% is not particularly rare.

- Directly connecting the patient's cognitive symptoms with the lesions is difficult, as the patient did not survive long enough for treatment response measurements. Exploration of localization of lesions in context of the patient's symptoms would have strengthened this assertion given the global deficits reported in the context of relative focal lesions. Additional discussion of neuroimaging findings in other patients to contextualize this patient's findings would also be helpful for readers to understand significance of results.
- Use of reference 22 source from brain MRI abnormality frequency in Discussion is inappropriate; that study was only examining patients with symptomatic lesions. Studies with unselected cohorts would be more appropriate. In those, symptomatic lesions are uncommon (<10%) and are likely more reflective of general epidemiologic data.
- In table 1, reference 17 is counted twice in "Seizure". Reference 26 is counted twice in "Cranial Nerve Involvement". This needs to be addressed or corrected.
- In table 2, reference 33 is a systematic review of 137 cases AND a case series of 3 new cases, so unclear why not included in Table 1. This needs to be addressed or corrected.
- In table 2, reference 16 includes in its systematic review cases lists in Table (ie. references 22 and 23). This is misleading to the reader who will think that a greater number of unique cases exist in the literature than are actually present.

Is the background of the case's history and progression described in sufficient detail?
Partly

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?
Partly

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?
Partly

Is the case presented with sufficient detail to be useful for other practitioners?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Pediatric Rheumatology, Craniofacial Scleroderma

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 25 October 2023

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The authors present a case with clinical features of linear scleroderma (LS) presenting with behavioral symptoms that can be seen with a medial prefrontal syndrome. However, the presentation as described does not contain details or test results that would have confirmed an association of his LS and his psychiatric manifestations. While a connection is conceivable, in this case it is circumstantial.

Re. Sufficient detail in history/exam/testing:
Changes associated with scleroderma are often insidious and develop over a long time - just like the scar - and therefore a 2-month history of behavioral changes should be clarified. Was the behavior change never noted or was it just worse in the last 2-months before he presented, or did he have seizures (focal seizures arising from the right frontal or temporal region which do not need to have motor features) related to the lesions which changed his behavior more abruptly, possibly as a postictal effect? It was not mentioned how much alcohol the patient consumed and whether there was a h/o alcoholism (esp in light of the low vit B12 level). Thyroid function tests are not listed, though thyroid disorders would be a much more common reason for behavioral changes. Furthermore, a psychiatric assessment is not mentioned to determine whether there may have been a psychiatric component, such as depression. Regarding the MRI, I doubt that there is vasogenic edema as there is no compression of the adjacent sulci or ventricle and no response to treatment with steroids. Typically, there is not much or any edema in brain lesions associated with LS, rather gliosis (however, vasogenic edema would be expected for a neoplastic process). Lastly, and importantly, there was no functional test mentioned that looked at the impact of the lesion in the right frontal lobe (e.g. EEG showing right frontal slowing or PET showing metabolic abnormalities in that area), therefore I believe the authors cannot assume or maintain that the the lesion which is relatively small and the behavior are connected.

Re. sufficient discussion of findings: I believe the patient has LS, but I think the authors have not not proven a causal relationship of behavior and the right frontal lesion by missing crucial historical findings, lab results and tests. At this point it is an association of features that may or may not be related which does not justify the claim that this is the first case of LS with a medial prefrontal syndrome.

I do not think that the Table 2 is valid unless the authors take care to sort out which cases are repeated in each of the systematic reviews and case series - as especially the systematic reviews accumulate the same cases from the literature. As far as I can tell the authors haven't done this, yet. Table 1 is also not valid as it stands because it lists and counts the same case twice under "Seizure" (17) and another case twice under "Cranial nerve involvement" (26) - this may be an oversight or warrants explanation.

Re. sufficient detail for other practitioners: I think the case and the pictures of scalp and MRI could be used for a discussion of LS with intracranial involvement, as well as a general discussion of neurological findings in these cases.

Is the background of the case's history and progression described in sufficient detail?

Partly

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?
Partly

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?
Partly

Is the case presented with sufficient detail to be useful for other practitioners?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Neurology, epilepsy, publication on Parry-Romberg syndrome

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.