Egyptian Rheumatology and Rehabilitation

CASE REPORT

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Generalized lymphadenopathy as an initial presentation of systemic lupus erythematosus: case report and review of the literature

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Abstract

Background Systemic lupus erythematosus (SLE) is a chronic multisystemic autoimmune disorder with a wide array of clinical manifestations. Lymphadenopathy is occasionally observed in patients with SLE, and although it is sometimes a feature of active disease, it is rarely the initial presenting feature at the time of diagnosis.

Case presentation We report the case of a 35-year-old woman with clinical features of generalized lymphadenopathy, fatigue, fever, and malaise of approximately 3 months duration with no other constitutional disorders or systemic involvement suggestive of SLE.

Despite extensive laboratory, radiological, and histological evaluations for malignancies and infectious causes of generalized lymphadenopathy, all results returned normal. About a month later, she developed inflammatory polyarthritis, with a markedly elevated erythrocyte sedimentation rate (ESR) of 120 mm/h, and a subsequent serologic workup confirmed the diagnosis of SLE.

Autoimmune serology testing revealed positive results for various antibodies, including antinuclear antibody (ANA) at a titre of 1:5120, homogenous and speckled pattern, anti-Sm, anti-dsDNA, U1-snRNP, Ku, SSA-AntiRo, SSB-AntiLa, anti-SM/RNP, anti-Histone, ribosomal-p protein, and anti-nucleosome antibodies. The diagnosis of SLE was established using the 2019 European League Against Rheumatism/American College of Rheumatology (EULAR/ ACR) criteria.

She was on oral prednisolone, hydroxychloroquine, and calcium/vitamin D3 tablets. The patient improved remarkably, all swollen lymph nodes regressed spontaneously and she had no further need for a hematology review.

Conclusion While similar cases have been reported in Europe and some parts of Asia, in Africa, a careful search of the literature revealed that such cases have been reported only from Egypt in North Africa and not from other parts of the continent; hence, this case report highlights the importance of recognizing atypical presentations of SLE to improve awareness and diagnosis in different regions.

Keywords SLE, Lymphadenopathy, Initial, Nigeria

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Background

Systemic lupus erythematosus (SLE) is a chronic multisystemic autoimmune disorder with a broad spectrum of clinical manifestations and a vaguely understood etiology [1]. Generalized lymphadenopathy can be caused by various conditions, including infections, autoimmune diseases (such as SLE, Sjogren syndrome, dermatomyositis, and rheumatoid arthritis), malignancies, storage diseases,

and drug reactions [2]. The diagnosis of SLE according to the American College of Rheumatology (ACR) criteria [3] must include at least four or more of the 11 diagnostic features, none of which include lymphadenopathy. The 2019 EULAR/ ACR and Systemic Lupus International Collaborating Clinics (SLICC) criteria also have no inclusion of lymphadenopathy among their diagnostic criteria [4, 5].

The reported frequency of lymphadenopathy in SLE patients is estimated to range between 25 and 50% [6, 7]. There are a number of case reports suggesting that generalized lymphadenopathy may be the first clinical feature of SLE [6–11], and, at other times, a part of the other constellation of the clinical features of SLE [12–14]. However, this has not been reported in Nigeria.

We present the case of a 35-year-old woman with painless generalized lymphadenopathy as the initial presenting complaint and an eventual diagnosis of SLE.

Case presentation

A 35-year-old Nigerian woman, married with 2 children, presented to the hospital with complaints of painless generalized lymphadenopathy of 3 months duration, along with worsening fatigue, recurrent fever, and malaise. There was no history of skin rashes, recurrent oral ulcers, photosensitivity, or other features suggestive of systemic autoimmune diseases at the time. The fever was described as low-grade intermittent, with no chills or rigors, and despite the use of several over-the-counter antipyretics, it persisted.

She had no significant past medical history and no family history suggestive of rheumatic or autoimmune illnesses. She was a teetotaler and never smoked cigarettes, and there was no history of use of tobacco or other recreational drugs in any form. In addition, there was no history of recurrent spontaneous first-trimester pregnancy loss.

Initially, she was evaluated by the hematologist for possible lymphoma; however, a month later, she developed inflammatory joint pain mainly in both knees and the small joints of the hands, with early morning stiffness occurring on most days of the week, lasting up to 1 h before gradually receding. She was then referred to a rheumatologist, especially as previous investigations had not led to a definitive diagnosis.

Physical examination revealed an otherwise healthy-looking young woman with vital signs as outlined [pulse rate: 92 beats per minute, normal volume and regular, respiratory rate: 20 cycles per minute, axillary temperature: 38.4 °C, blood pressure: 122/78 mmHg (sitting position-left arm)]. She had multiple enlarged, painless lymph nodes in the cervical, axillary, and inguinal regions, they were freely mobile and not matted, and the largest of them measured 4 × 2 cm. Arthritis was evidenced by joint tenderness and swelling involving both knees; the 1st to 3rd metacarpophalangeal (MCP) joints on the left hand; the wrist; and the 2nd, 4th, and 5th MCP and proximal interphalangeal joints on the right hand. There was a positive squeeze test in both hands, and no deformities were noted at the time of review. All other systemic examinations were normal. Her initial investigation results are presented in Table 1.

The elevated total protein level was believed to be caused by increased production of immunoglobulins, particularly immunoglobulin G, which is often observed in SLE and other autoimmune diseases. The low serum albumin concentration is explained by the fact that it is a negative acute-phase reactant.

Table 1 Complete blood count and other relevant investigations

Complete blood count	Metabolic panel	Acute phase reactants and viral screenings	Urine analysis
TWBC; 9.27 (4–10 × 10^9/L)	Sodium: 138 mmol/L (136–145)	[a]ESR: 120 mm/h (1–20)	Appearance: clear and yellow
Neutrophil: 48.6% (40–80)	Potassium:4.3 mmmol/L (3.5–5.0)	CRP: 3.1 mg/L(1–10)	Specific gravity: 1.030
Lymphocytes: 40.3% (20–40)	Bicarbonate: 19 mmol/L (18–32)	HBsAg: negative	pH: 7.5
Monocytes: 5.0% (2–10)	Chloride: 104 mmol/L (96–110)	HIV: negative	Protein: negative
Eosinophils: 3.2% (1–6)	Urea: 30 mg/dL (10–50)	Anti-HCV: negative	Blood: negative
Basophil:2.9% (0–2)	Creatinine: 0.9 mg/dL (0.5–1.10)		Urobilinogen: normal
Haemoglobin: 10.6 g/dl (11.5–15.0)	Total protein: 9.11 g/dL (6.6–8.7)		Epithelial cells: scanty
Platelets: 282 (150–450 × 10^3/µL)	Albumin: 3.30 mg/dL (3.5–5.0)		RBC: absent
	Total bilirubin: 9.0 µmol/l (2–20)		Hemoglobin; negative
	Conj. Bilirubin: 3.4 µmol/l(0–8)		Casts: absent
	AST:35 µ/L(10–42)		Leucocyte esterase: negative
	ALT:28 µ/L(10–40)		Crystals: absent
	ALP:192 µ/L(40–120)		UPCR: 6 mg/mmol (0–15)

[a] Abnormally high value

Blood culture yielded no growth of organisms, microscopy for malaria parasites was negative, and further tests for a full sepsis workup, including tests for cytomegalovirus (CMV) and Epstein–Barr virus (EBV), were deferred due to financial constraints, as the costs of all investigations and treatments were all borne by the patient.

Venereal disease research laboratory (VDRL) tests for syphilis and Mantoux tests for tuberculosis were both negative and serum angiotensin-converting enzyme (ACE) was unremarkable. An excisional biopsy of one of the right cervical lymph nodes revealed histological features suggestive of a reactive lymph node (Fig. 1).

A chest computed tomography (CT) scan (Fig. 2) revealed bilateral multilevel axillary lymph nodes with additional findings of hepatomegaly (midclavicular craniocaudal diameter of 18 cm, normal range 15.5–16 cm). However, the liver echotexture was homogenous with regular margins, and no diffuse lesions were observed. In addition, the results of the human immunodeficiency virus (HIV) and hepatitis B and C screenings were all negative, as shown in Table 1.

Due to the unexplained constitutional symptoms, markedly elevated ESR, and the new onset inflammatory joint pain, an extractable nuclear antigen (ENA) panel, C3, C4 Complements, rheumatoid factor, and anti-CCP were requested. The latter two tests were negative, while the ENA panel and C3 and C4 complement results confirmed the diagnosis of lupus (Table 2). On the basis of the above, the diagnosis of SLE was established using the 2019 EULAR/ ACR criteria, which require a minimum of 10 points (patient had a cumulative score of 18, i.e., constitutional symptoms (fever); 2 points, arthritis domain; 6 points, low C3 and C4 complements; 4 points, SLE-specific antibodies; anti-smith 6 points) after fulfilling the entry criteria with an ANA titre of 1: 5120.

Disease activity was assessed using the Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic

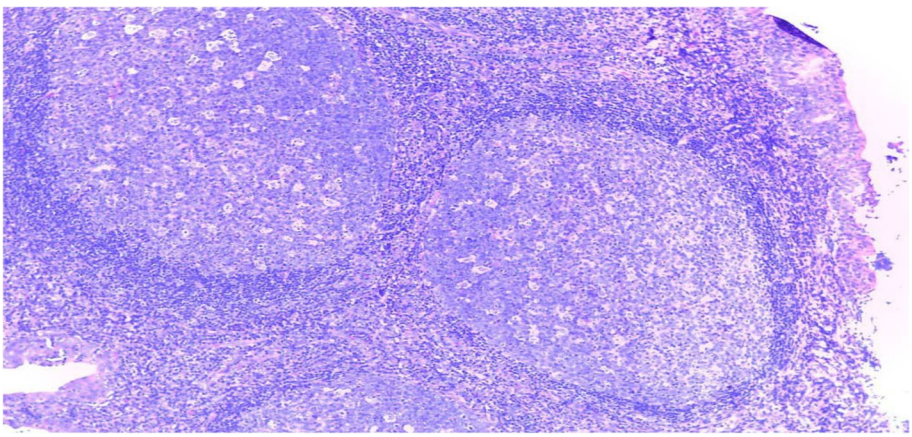

Fig. 1 Lymph node histology showing reactive follicular hyperplasia, lymphoid follicles with germinal centers identified, interfollicular areas not expanded, no neoplastic cells, or features of granulomatous inflammation are present

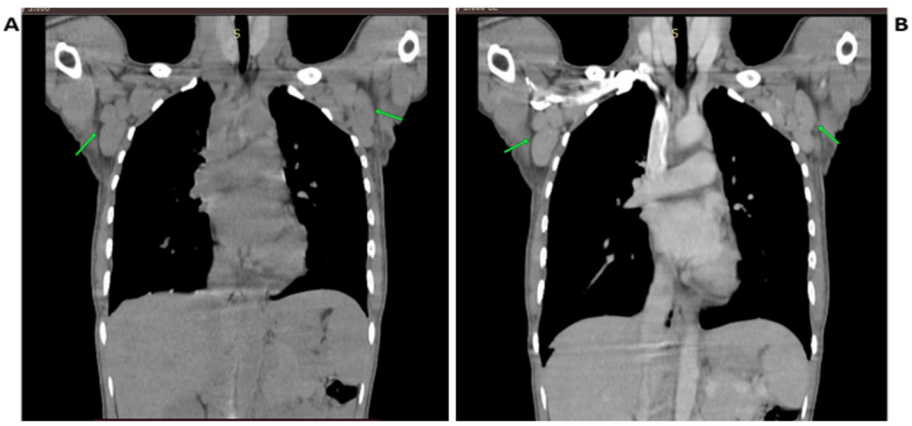

Fig. 2 Noncontrast (**A**) and contrast-enhanced (**B**) chest CT scans showing multiple enlarged axillary lymph nodes of varying sizes

Table 2 Antibody panel

Parameter	Result
ANA	1:5120 Homogenous and speckled
U1-snRNP	5.5(+++) positive
Ku	3.0(++) positive
Anti dsDNA	6.7(+++) positive
SS-A AntiRo 60	6.7(+++) positive
SS-B AntiLa	1.0(+/–) borderline
Anti Sm	7.3(+++) positive
Anti SM/RNP	7.7(+++) positive
Anti-Histon abs	1.3(+) positive
Ribosomal p-protein	3.1(++) positive
Nucleosom	4.8(++) positive
C3 complement	0.35 g/L (0.83–1.93) low
C4 complement	0.03 g/L (0.15–0.57) low

Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI). The patient had a baseline score of 5 (arthritis: 4 points, fever: 1 point). The SELENA-SLEDAI ranges from 0 to 105; and is categorized according to disease activity into the following groups: no activity (SLEDAI = 0), mild activity (SLEDAI = 1 to 5), moderate activity (SLEDAI = 6 to 10), high activity (SLEDAI = 11 to 19), and very high activity (SLEDAI ≥ 20) [15, 16]. Although screening for antiphospholipid antibodies (APLAs) is part of the baseline test for new SLE patients, our index patient had a low clinical likelihood for antiphospholipid syndrome (APS), as there was no prior history of obstetrics or thrombotic events; moreover, there was a need to prioritize all required investigations in a bid to reduce cost.

The patient was on oral hydroxychloroquine 200 mg BD (after an ophthalmology review), oral calcium 600 mg/vitamin D3 400 mg/day, and oral prednisolone 30 mg daily for the first month; and then gradually tapered to 10 mg daily. At the 6-week follow-up visit, her symptoms improved remarkably, the inflammatory joint pain resolved, lymph node swellings regressed spontaneously, and her fatigue reduced significantly; hence, she was able to resume her normal daily activities. The SELENA-SLEDAI score at 6 weeks was 0, and the ESR dropped from 120 mm/h at presentation to 30 mm/h. The patient's initial CRP was 3.1 mg/l (Table 1), and a repeat was not indicated, especially as it appears to be an unreliable marker of inflammation in SLE patients since its circulating levels can be modest or very low despite the presence of an ongoing extensive inflammation [17].

All the medications were well tolerated with no adverse effects, and the patient was quite satisfied with the treatment received, although she was eventually lost to follow-up. The reporting of this case conforms to CARE guidelines [18].

Discussion

The strength of this case lies in its novelty and the fact that it has not been reported among native black women from most parts of Africa (Egypt being the exception) where there are several tropical diseases that can mimic generalized lymphadenopathy. Additionally, lymphadenopathy is not routinely included in the diagnostic workup for SLE patients despite being found in the real world. A major limitation of this report is that investigations of the causes of generalized lymphadenopathy in this patient were not complete due to financial constraints, and some baseline tests for new SLE patients (e.g., APLAs) were not performed.

Generalized lymphadenopathy is defined as the enlargement of two or more noncontiguous groups of lymph nodes. Common causes of generalized lymphadenopathy include viral infections such as acquired immune deficiency syndrome, rubella, and infectious mononucleosis. Important bacterial causes include tuberculosis brucellosis, syphilis, and cat scratch disease [2]. Storage diseases (such as Gaucher disease) and certain drug reactions are among the other known causes of lymphadenopathy [2].

Sarcoidosis, lymphomas, autoimmune diseases, and Kikuchi-Fujimoto disease are among the major noninfectious causes of lymphadenopathy [9]. Less common causes include systemic amyloidosis, and some rare conditions, such as Kimura disease and Castleman's disease [2]. Laboratory investigations to rule out pertinent differential diagnoses are vital, especially basic tests such as ESR, considering that markedly elevated ESRs are often found in malignancies, lymphomas, and systemic autoimmune conditions, including SLE [19]. Lymph node biopsy is often needed to establish a histological diagnosis.

The prevalence of lymphadenopathy in SLE patients gathered from epidemiological data is estimated to be between 33 and 69% [20, 21]. Lymphadenopathy can occur during periods of increased disease activity or rarely at the beginning of the illness as the initial presenting sign; however, it is not included in the SLE classification criteria [4, 8, 11, 20]. In a retrospective study of about 90 SLE patients, 26% were found to have lymphadenopathy. In Africa, lymphadenopathy was found in 4% of an Egyptian SLE cohort [22]. Lymph nodes in SLE patients are commonly located in the cervical and axillary regions; and are often small, painless, soft, mobile, and not fixed to underlying structures [8]. Patients with SLE-related lymphadenopathy have a conceivably higher likelihood of presenting with accompanying constitutional features such as weight loss, malaise, fever, and night sweats; in addition; they may have low complement levels, increased titres of anti-dsDNA antibodies and hepatosplenomegaly [8, 23]. A biopsy becomes necessary when the extent and severity of lymphadenopathy

far exceeds that of lupus activity, and again if the patient has symptoms in other systems that make an alternative or coexisting diagnosis very likely.

In our index patient, most of the assumed classical features of SLE were absent. There were no mucocutaneous manifestations, or other features that often suggest systemic involvement of the disease. Clinical suspicion for SLE was raised when the patient recorded a markedly elevated ESR and then later developed inflammatory arthritis. SLE was confirmed by excluding other common aetiologic possibilities of diffuse enlarged lymph nodes such as tuberculosis, HIV, and lymphomas; and then the positive SLE-specific antibodies (anti-smith, anti-dsDNA) together with the presence of musculoskeletal symptoms which the patient had. This is similar to the case reported in Egypt of a 34-year-old female who presented with generalized lymphadenopathy and was eventually diagnosed with SLE, after being thoroughly investigated. However, she had more florid musculoskeletal and dermatological features around the time of presentation [22]. This is in keeping with the fact that lymphadenopathy can predate the more common features that typify the disease [9, 23]. Lupus lymphadenitis can be the first noticeable sign of an SLE flare, but common infections, lymphoma, and other systemic autoimmune conditions must be considered in all SLE patients with coexisting lymphadenopathy [23].

Other important differential diagnoses to consider include; Kikuchi-Fujimoto disease, sarcoidosis, and Castleman's disease. Sarcoidosis is a multisystem inflammatory disease whose exact etiology is not known. It predominantly affects the lungs and intrathoracic lymph nodes. The histological findings in SLE lymph node specimens are often nonspecific and consist of follicular hyperplasia with associated increased vascularity and scattered immunoblasts and plasma cells. The most consistent but variably present finding is often coagulative necrosis with hematoxylin bodies or reactive follicular hyperplasia; this too is rarely seen [24]. In sarcoidosis, the histological presentation most commonly consists of non-necrotizing granulomas [25]. The presence of non-caseating granulomas (NCGs) in the histology of affected organ tissues confirms the diagnosis [26]. These findings were not consistent with our patient's biopsy report. Although the presence of lymphadenopathy on chest CT may be suggestive, the serum angiotensin-converting enzyme (ACE) level was however normal.

Kikuchi disease is another differential diagnosis to consider. It is a rare, idiopathic, generally self-limiting cause of lymphadenitis [27]. The etiology of the disease is unknown although there may be some autoimmune basis. It can be triggered by infectious agents, including recently COVID-19, and there are reports that it can precede or coexist with SLE [27, 28]; it typically presents with painful unilateral cervical lymphadenopathy with or without other systemic symptoms and usually has a benign course. Lymph node biopsy may reveal single or multiple necrotic foci, and histiocytic cellular infiltration, without granulocytic involvement [28]. The absence

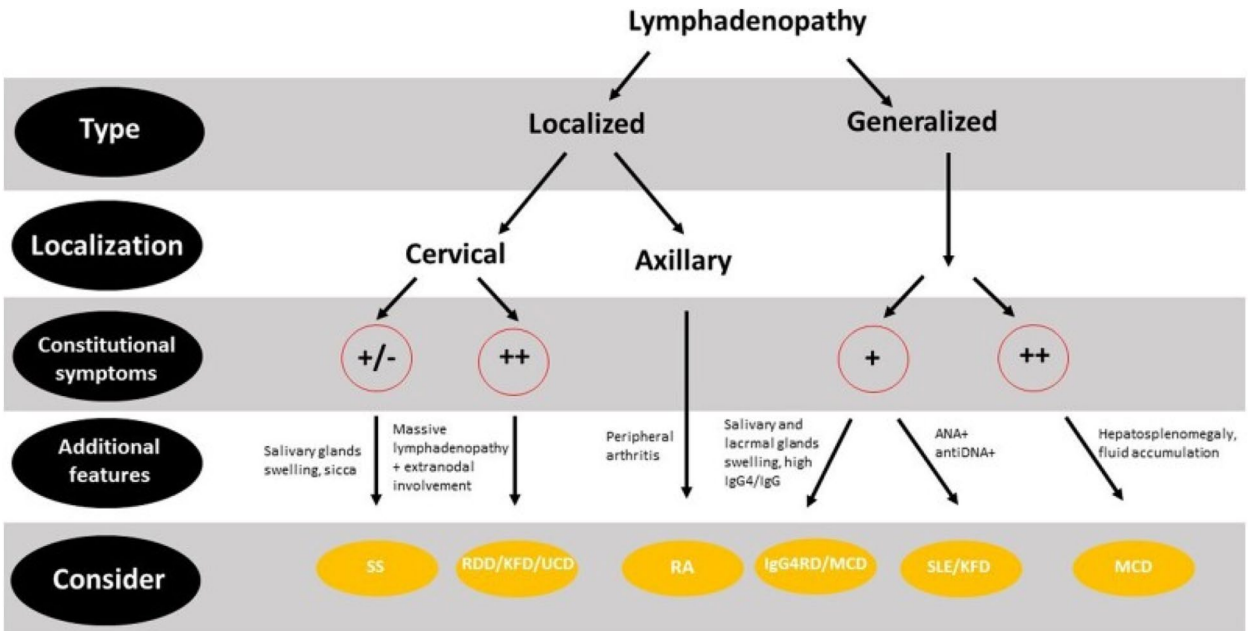

Fig. 3 Flow chart for the interpretation of lymphadenopathy in rheumatological diseases (adapted from Rodolfi S, et al. [20]) SS:Sjoren syndrome; KFD: Kikuchi Fujimoto disease; RDD: Rosai Dorfman disease; IgG4RD: IgG4-related disease; UCD: unicentric Castleman disease; RA: Rheumatoid arthritis; MCD: multicentric Castleman disease

of these histologic findings in our patient ruled out the diagnosis of Kikuchi disease.

Castleman's disease (CD) is a rare group of lymphoproliferative disorders that can involve unicentric or multicentric regions of lymph nodes (Fig. 3). Its etiology is not fully known, although some variants of the disease have been linked with human herpes virus 8 (HHV-8). The clinical features of CD depend on the subtype and may include; flu-like symptoms, cough, fatigue, fever, numbness and weakness from nerve damage, night sweats, weight loss, and enlarged lymph nodes. Histology may reveal prominent vascular proliferation, with increased plasma cells and hyalinization of the vessel walls [29]. In contrast, histology results of the index case revealed only reactive lymph node changes.

Conclusion

Generalized lymphadenopathy may occur in patients with SLE, sometimes as the initial and rarely the only presenting feature of the disease. Although it is considered to be a feature of an active disease, it is not included as a component in any of the classification criteria of the disease.

Clinicians should be aware that SLE is among the differential diagnoses of generalized lymphadenopathy; hence, a full immunological panel for rheumatological disorders should be requested when faced with such a clinical scenario, especially if these findings are noted in young females of reproductive age, who have an unusually elevated ESR.

Abbreviations

ACE	Angiotensin converting enzyme
ACR	American College of Rheumatology
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ANA	Antinuclear antibody
Anti-CCP	Anti-cyclic citrullinated peptide
Anti-dsDNA	Anti-double-stranded DNA
APLAs	Antiphospholipid antibodies
APS	Antiphospholipid syndrome
AST	Aspartate transaminase
CMV	Cytomegalovirus
CRP	C-reactive protein
CT	Computed tomography
EBV	Epstein–Barr virus
ENA	Extractable nuclear antigen
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
MCP	Metacarpophalangeal
PIP	Proximal interphalangeal
RBC	Red blood cell
SELENA	Safety of Estrogens in Lupus Erythematosus National Assessment
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SLE	Systemic lupus erythematous
SLICC	Systemic Lupus International Collaborating Clinics
TWBC	Total white blood cell count
VDRL	Venereal Disease Research Laboratory test

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Authors' contributions

HBO and HHA made the diagnosis. HJE and EOB continued with outpatient follow-up care. HJE also wrote the manuscript, and OOA supervised the case and edited the initial write-up. All the authors read and approved the final manuscript.

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Declarations

Ethics approval and consent to participate

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Consent for publication

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Competing interests

The authors declare that they have no competing interests.

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