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Case Report: Monoclonal Gammopathy of Undetermined Significance is Associated with *Loa loa* Infection

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Abstract. A 63-year-old woman who migrated from Nigeria to the United States was found to have an elevated total serum protein, anemia, and eosinophilia. Serum protein electrophoresis (SPEP) and serum protein immunofixation electrophoresis (SPIFE) demonstrated monoclonal immunoglobulin G (IgG) κ restricted bands (IgG 3,820 mg/dL; κ/λ ratio 4.47), indicative of monoclonal gammopathy of unknown significance (MGUS). A rapid diagnostic test (RDT) for malaria was positive for *Plasmodium falciparum* (BinaxNOW®; Alere Scarborough Inc., Scarborough, ME). Giemsa-stained blood smears were negative for malarial parasites, however, *Loa loa* microfilariae were identified. Reverse transcription polymerase chain reaction for *P. falciparum*, *Plasmodium ovale*, *Plasmodium malariae*, and *Plasmodium vivax* yielded a negative result. She was treated for loiasis with diethylcarbamazine and received no malaria medication. Treatment resulted in a resolution of the microfilaremia and eosinophilia, a negative RDT for malaria, and marked reduction in the monoclonal gammopathy. This is the first reported human case of MGUS associated with loiasis and its resolution after antiparasitic treatment.

INTRODUCTION

Monoclonal gammopathy (MG) is a disorder where elevated abnormal serum protein levels are observed because of increased monoclonal immunoglobulins.[1,2] It likely results from chronic antigenic stimulation, leading to abnormal B cell clonal expansion, accumulation of this proliferating B cell or plasma cell clone within the bone marrow, and resulting in increased monoclonal immunoglobulin production.[3–5] Monoclonal gammopathy has the potential for malignant transformation (e.g., multiple myeloma, Waldenström's macroglobulinemia, and plasma cell leukemia) or could remain in a premalignant state for a lifetime, known as MG of undetermined significance (MGUS).[1,2] Although polyclonal gamma globulin elevations generally result from reactive, inflammatory, or infectious processes,[2] monoclonal gammaglobulin elevations have been observed in the setting of cytomegalovirus,[6] human immunodeficiency virus,[7] visceral leishmaniasis,[8] disseminated *Staphylococcus aureus* infection,[9] hepatitis C virus,[10] human herpesvirus 8,[10] potentially Epstein-Barr virus,[4] and *Helicobacter pylori*.[4]

Loa loa, the causative agent of loiasis, is a filarial nematode that infects 10 million people, and another 30 million are at risk of infection.[11–13] It is endemic to West and Central Africa.[11–17] In non-endemic regions, loiasis is diagnosed in immigrants or returning travelers.[18,19] Clinical diagnosis is often based on history and clinical manifestations and is confirmed by demonstrating microfilariae in peripheral blood usually accompanied by eosinophilia.[11,20–23] Although elevated polyclonal Ig levels have been demonstrated in human loiasis,[24–26] there are no reports of M-protein elevation or its resolution on treatment. However, MG has been described in *Diroflaria immitis* infection in a canine host that resolved after treatment.[27] Herein, we document the resolution of MGUS after treatment of *Loa loa* infection.

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CASE DESCRIPTION

A 63-year-old Nigerian woman immigrated to the United States 4 years before this presentation.

She lived in Lagos but she also lived in Ibadan and Ila Orangun, where she had ventured into the forest in her youth where there is a nearby Old Oyo National Park, Kainji Lake National Park, and River Moshi. She had multiple medical problems and was being treated for latent tuberculosis. She presented for a routine follow-up and was asymptomatic. Vital signs and physical examination were within normal limits and there was no evidence of peripheral edema, rashes, or jaundice.

Laboratory investigation. A random glucose was elevated at 233 mg/dL, blood urea nitrogen was 41, and creatinine 1.3. The total serum protein level was 9.5 g/dL with an increased albumin–gammaglobulin gap (5.6 g/dL). There was mild anemia (Hemoglobin 12.1 g/dL) and marked eosinophilia (34.3%). These findings resulted in additional testing to evaluate the patient for both an immunoproliferative disorder and a parasitic infection.

Serum protein electrophoresis electrophoretogram (Figure 1A) and SPEP quantitative values (Table 1) showed elevated total protein (9.0 g/dL; reference range 6.0–8.3 g/dL), β globulin fraction (1.3 g/dL; reference range 0.5–1.0 g/dL), γ globulin fraction (2.9 g/dL; reference range 0.6–1.6 g/dL), and an abnormal M-spike (0.8 g/dL; reference range 0.0–0.0 g/dL); albumin, albumin/globulin ratio, α_1 globulin fraction, α_2 globulin fraction were within their respective reference ranges. Serum protein immunofixation electrophoresis calculated peak areas (Table 2) showed elevated IgG (3,820 mg/dL; reference range 694–1,618 mg/dL), κ free light chains (16.90 mg/dL; reference range 0.33–1.94 mg/dL), λ free light chains (3.78 mg/dL; reference range 0.57–2.63 mg/dL), and κ/λ ratio (4.47; reference range: 0.26–1.65); immunoglobulin A and immunoglobulin M levels were within their respective reference ranges. These findings were consistent with a MG.

A rapid diagnostic test (RDT) for malaria (BinaxNOW) was positive for *P. falciparum* (Figure 2A). Giemsa-stained thin and thick blood smears were negative for malaria parasites. A blood

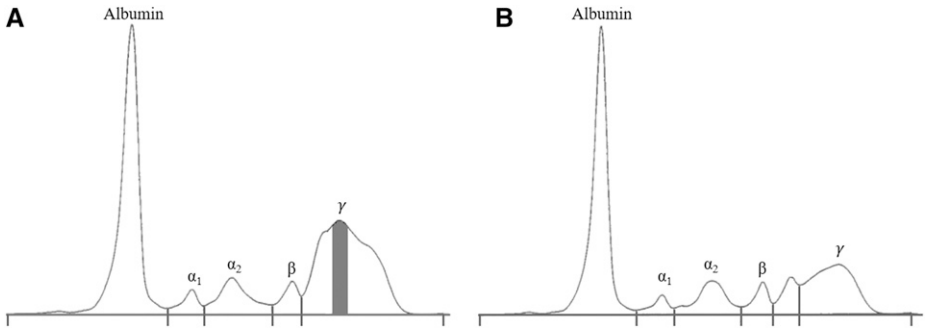

FIGURE 1. (**A**) Serum protein electrophoresis electrophoretogram before diethylcarbamazine (DEC) treatment revealing a broad M-component in the γ globulin region. (**B**) Serum protein electrophoresis electrophoretogram after the completion of the DEC treatment regimen revealing resolution of the M-component in the γ globulin region.

sample was sent to a reference laboratory for reverse transcription polymerase chain reaction (RT-PCR) for *P. falciparum*, *Plasmodium ovale*, *Plasmodium malariae*, and *Plasmodium vivax*, which yielded a negative result. Interestingly, the blood smears revealed microfilariae consistent with *L. loa* (Figure 3). Before initiating the treatment of loiasis, serologic testing for onchocerciasis was performed at the National Institutes of Health, which was negative.

Treatment of loiasis. The patient was treated for loiasis with a 21-day diethylcarbamazine (DEC) regimen. No malaria treatment was given. She was admitted to the hospital for monitoring during the first 5 days of her therapy. On day 1, she received 50 mg of DEC and 40 mg of prednisone to prevent a Jarisch–Herxheimer–like reaction.[28] Overnight, she experienced some mild chest pain, which resolved spontaneously after 2 hours. On day 2, her dose was increased to 50 mg *ter in die* (TID; three times a day) (150 mg total) and prednisone was decreased to 20 mg (once a day). On day 3, DEC was increased to 100 mg TID (300 mg total) and the patient experienced some right-sided shoulder pain and fatigue, which resolved by the end of the day. She had no other side effects during her admission or during the course of her treatment. On day 5 DEC was increased to 200 mg TID (600 mg total). She was discharged on day 5 and continued to take 200 mg TID DEC at home for 16 more days.

The complete blood counts with differential from about 686 days before treatment to about 120 days after the completion of treatment of loiasis are summarized in Table 2. She developed leukocytosis (14.97 K/μL; reference range: 4.5–10.9 K/μL) by day 3 of her admission, likely secondary to prednisone, however, the white blood cell count trended down over the next several days (7.91 K/μL; reference range: 4.5–10.9 K/μL). Her eosinophilia markedly improved on day 2 of treatment (3.1% eosinophils; reference range 0–8.6%) but then as expected because of worm death, increased to a peak of 25.0% at day 5. The eosinophilia then declined to 9.3% at 45 days posttreatment (Table 2).

The SPEP electrophoretogram (Figure 1B) and SPEP (Table 1) after treatment demonstrated a reduction in total protein (8.4 g/dL; reference range 6.0–8.3 g/dL), β globulin fraction (1.0 g/dL; reference range 0.5–1.0 g/dL), and γ globulin fraction (2.0 g/dL; reference range 0.6–1.6 g/dL), with resolution of the abnormal M-spike. Serum protein immunofixation electrophoresis–calculated peak areas (Table 1) demonstrated a reduced IgG (2,370 mg/dL), κ-free light chains (9.92 mg/dL), λ-free light chains (3.46 mg/dL), and κ/λ ratio (2.87); IgA and IgM levels were within their respective reference ranges. After the completion of treatment of loiasis, it was noted that the antinuclear antibody was positive with a titer of 1:80 and speckled pattern by an indirect fluorescent antibody test, using HEp-2 cells, and positive anti-Jo-1 by a multiplex bead immunoassay. The rheumatoid factor was normal.

Giemsa-stained blood smears were negative for malaria. The RDT for malaria (BinaxNOW) which had been positive

TABLE 1
Results of SPEP and SPIFE relative to treatment of loiasis

	Diagnostic parameter	Reference range	Pretreatment	Posttreatment
SPEP	Total protein	**6.0–8.3 g/dL**	**9.0**	8.4
	Albumin/globulin ratio	0.8–2.0 ratio	0.7	1.0
	Albumin	3.6–5.5 g/dL	3.8	4.2
	α1 globulin fraction	0.1–0.4 g/dL	0.3	0.3
	α2 globulin fraction	0.5–1.0 g/dL	0.8	0.9
	β globulin fraction	0.5–1.1 g/dL	**1.3**	1.0
	γ globulin fraction	0.6–1.6g/dL	**2.9**	**2.0**
	M-spike	0.0–0.0 g/dL	**0.8**	N/A
SPIFE	Immunoglobulin G	694–1,618 mg/dL	**3,820**	**2,370**
	Immunoglobulin A	68–378 mg/dL	112	134
	Immunoglobulin M	40–230 mg/dL	92	112
	Immunoglobulin κ	0.33–1.94 mg/dL	**16.90**	**9.92**
	Immunoglobulin λ	0.57–2.63 mg/dL	**3.78**	**3.46**
	κ/λ ratio	0.26–1.65 ratio	**4.47**	**2.87**

N/A = not applicable; SPEP = serum protein electrophoresis; SPIFE = serum protein immunofixation electrophoresis.
* Bold values exceed their respective reference ranges.

TABLE 2
Complete blood counts on representative clinic visit days and during hospitalization (bold) for treatment of loiasis

Days	1	98	155	175	177	224	286
Diagnostic parameter (reference range)							
RBC (4.2–5.40 M/μL)	4.06	3.72	4.07	**3.45**	**3.72**	3.83	4.36
Hgb (12.0–16.0 g/dL)	12.1	11.1	12.0	**10.6**	**11.1**	11.9	13.1
Hct (37.0–47.0%)	36.5	34.1	37.6	**30.9**	**33.9**	35.5	38.6
Plt (130–400 K/μL)	182	228	228	**222**	**217**	188	181
WBC (4.5–10.9 K/μL)	9.42	9.58	10.04	**10.41**	**14.97**	7.91	7.21
Neut (38.7–60.3%)	39.4	40.9	41.8	**35.6**	**53.0**	43.2	50.0
Lymph (22.4–49.0%)	21.6	28.5	24.1	**29.8**	**24.9**	40.5	34.1
Mono (2.4–9.2%)	3.3	3.3	3.0	**3.8**	**4.0**	4.1	4.1
Eos (0–8.6%)	34.3	25.1	28.2	**29.0**	**16.6**	9.3	9.3
Baso (0–1.0%)	0.2	0.4	0.3	**0.1**	**0.3**	0.4	0.3

Baso = basophils; Eos = eosinophils; Hct = hematocrit; Hgb = hemoglobin; Lymph = lymphocytes; Mono = monocytes; Neut = neutrophils; Plt = platelets; RBC = red blood cells; WBC = white blood cells.

was repeated and showed complete resolution of the T1 (*P. falciparum*) band (Figure 2B).

DISCUSSION

We have described the clinical and laboratory features of the first human patient with MGUS, eosinophilia, and incidentally diagnosed loiasis. This 63-year-old Nigerian immigrant to the United States was found to have anemia, elevated total serum protein, an increased albumin-gammaglobulin gap, and a significant eosinophilia. Serum protein electrophoresis and SPIFE demonstrated weak monoclonal IgG κ restricted bands. A whole blood RDT for malaria was positive for *P. falciparum* (BinaxNOW). Giemsa-stained thin and thick blood smears were negative for malaria parasites, however, unexpectedly, *L. loa* microfilariae were identified. Reverse transcriptase polymerase chain reaction for *P. falciparum*, *P. ovale*, *P. malariae*, and *P. vivax* yielded a negative result, as did a serologic test for onchocerciasis. The patient had eosinophilia but lacked any specific symptoms attributable to loiasis.[11,14–17,19] Those that are asymptomatic but microfilaremic are at an increased risk for morbidity and mortality.[16] Some patients with loiasis remain amicrofilaremic,[29] which led to the development of PCR-based tests that are not available for clinical use.[30]

Microscopic examination of Giemsa-stained peripheral blood smears is the gold standard for laboratory diagnosis of malaria, however, this technique is not perfect and depends largely on the experience of the microscopist.[31] This has led to the development of newer tests that are less labor intensive and do not require vast expertise, patience, and interpretation, although species identification by microscopy is still required. Rapid diagnostic tests for malaria are adjunct diagnostic modalities that are increasingly being used to rapidly screen for malaria.[31–34] The BinaxNOW Malaria (Alere Scarborough, Inc., Scarborough, ME) is the only in vitro assay licensed for use in the United States for this purpose;[35] it is based on an immunochromatographic technique to qualitatively identify circulating *Plasmodium* antigens in whole blood; and results are available in as little as 15 min.[31,35] Our patient was also tested for malaria by RT-PCR, which yielded a negative result, suggesting that the RDT result was falsely positive. We, therefore, conclude that the false-positive RDT result was due to interference from *L. loa* antigens, anti-*L. loa* antibodies or monoclonal gammaglobulins.

Treatment of loiasis resulted in complete resolution of loiasis, MGUS, and eosinophilia. We also encountered a false-positive RDT for malaria during the patient's workup that also resolved on completion of the treatment. This case illustrates an aberrant immune response to an infection manifesting as MG. The implications for not properly identifying the specific

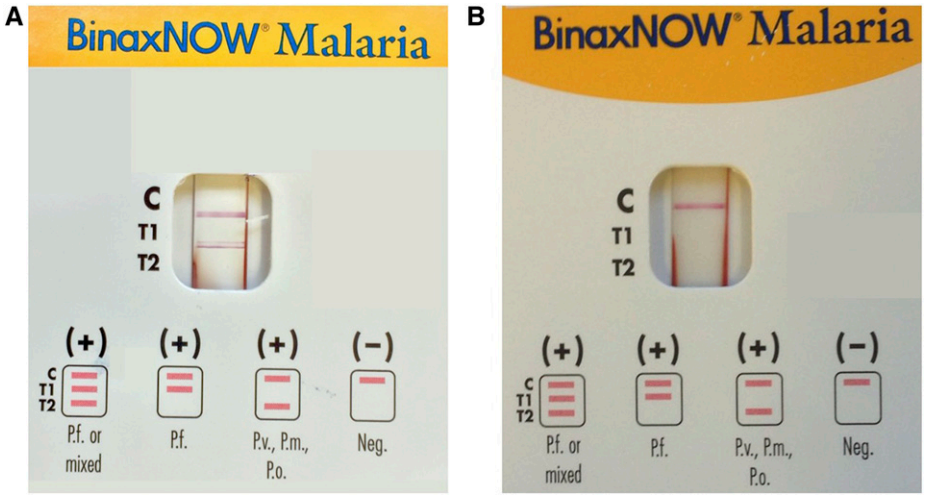

FIGURE 2. (**A**) Malaria rapid diagnostic test (RDT) (BinaxNOW) card of assay performed before diethylcarbamazine treatment showing positive result for *Plasmodium falciparum*. (**B**) Post-treatment RDT card showing negative result. This figure appears in color at www.ajtmh.org.

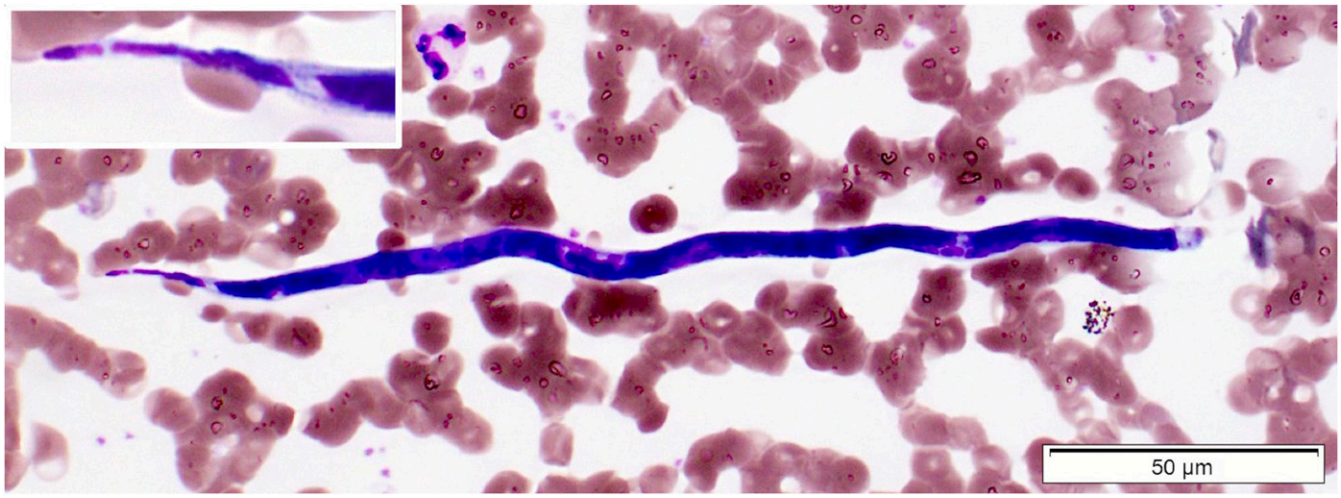

FIGURE 3. Giemsa-stained peripheral blood smear showing *Loa loa* microfilariae with poorly stained pale blue sheath and caudal nuclei extending to the tip of the tail (inset). This figure appears in color at www.ajtmh.org.

underlying cause of MGUS could lead to increased morbidity and mortality—including unnecessary investigations and invasive procedures (e.g., bone marrow biopsy), the potential for malignant transformation, and increased susceptibility of bacterial and viral infections.[36–38] In addition, this case demonstrates that rapid malaria antigen assays can yield false-positive results when a helminth-infected patient develops an infection-mediated gammopathy.

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Ethics: The patient was treated under a protocol approved by the Institutional Review Board (IRB # 1071388-1; FDA IND # 57,944). Informed consent was obtained from the patient for this article.

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