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Reactivation of Chagas Disease in a Patient With an Autoimmune Rheumatic Disease: Case Report and Review of the Literature

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Reactivation of Chagas disease has been described in immunosuppressed patients, but there is a paucity of literature describing reactivation in patients on immunosuppressive therapies for the treatment of autoimmune rheumatic diseases. We describe a case of Chagas disease reactivation in a woman taking azathioprine and prednisone for limited cutaneous systemic sclerosis (lcSSc). Reactivation manifested as indurated and erythematous cutaneous nodules. Sequencing of a skin biopsy specimen confirmed the diagnosis of Chagas disease. She was treated with benznidazole with clinical improvement in the cutaneous lesions. However, her clinical course was complicated and included disseminated CMV disease and subsequent septic shock due to bacteremia. Our case and review of the literature highlight that screening for Chagas disease should be strongly considered for patients who will undergo immunosuppression for treatment of autoimmune disease if epidemiologically indicated.

Keywords. Chagas disease; autoimmune rheumatic disease.

PATIENT CASE

An 86-year-old woman developed painful subcutaneous nodules on her medial thighs and left upper extremity (Figure 1A, B). Over the ensuing 2 months, the nodules enlarged and became more indurated, erythematous, and painful. She also developed night sweats, fatigue, diarrhea, anorexia, and weight loss.

The patient had a history of poorly controlled diabetes mellitus and limited cutaneous systemic sclerosis (lcSSc; a multisystem autoimmune rheumatic disease), manifested as pulmonary hypertension and Reynaud's syndrome. Eight months before admission, she was diagnosed with tachy-brady syndrome, requiring a pacemaker. Echocardiogram at that time showed a dilated right ventricle with elevated pressures, preservation of left ventricle ejection fraction, and no wall motion abnormalities or apical aneurysms. For management of lcSSc, she had been on long-standing azathioprine (100 mg/d). Prednisone (15 mg/d) was added 3 months before the current presentation for management of a diagnosis of retinal vasculitis.

The patient was born and raised in a rural mountain village near Trujillo, Venezuela. As a child, she lived in a mud hut and cared for many animals including chickens, dogs, and cats. At 20 years of age, she emigrated to the United States. She traveled back to Venezuela only once at 70 years of age, and otherwise denied international travel.

She was admitted to the hospital, where she was initially afebrile and hemodynamically stable. Physical exam showed no mucosal abnormalities or regional lymphadenopathy. White blood cell count was 4.4 K/μL with profound lymphopenia (absolute lymphocytes 0.2 K/μL), hemoglobin 11.5 g/dL, and platelets 126 K/μL. Kidney and liver function were normal. An HIV antigen/antibody test was negative. *Strongyloides* serology was negative. Computed tomography scan showed scattered bilateral pulmonary nodules; normal caliber esophagus, small bowel, and large bowel; and inflammation in the ascending colon. Contrast-enhanced brain magnetic resonance imaging was normal.

Biopsy of the skin nodules (Figure 2A, B) showed a lymphohistiocytic infiltrate in the superficial and deep dermis with round intracellular organisms noted on hematoxylin/eosin stain. Periodic acid-Schiff-diastase, Gomori methenamine silver (GMS), Fite, and gram stains did not highlight the organisms. However, structures resembling kinetoplasts were minimally accentuated on GMS stain. Bacterial, fungal, and acid-fast bacillus cultures were ultimately negative. Serology for *Trypanosoma cruzi* (performed at Mayo Clinic Laboratories) was positive by both enzyme-linked immunosorbent assay and a lateral flow assay. A Giemsa-stained smear of peripheral blood (buffy coat) was negative, and real-time

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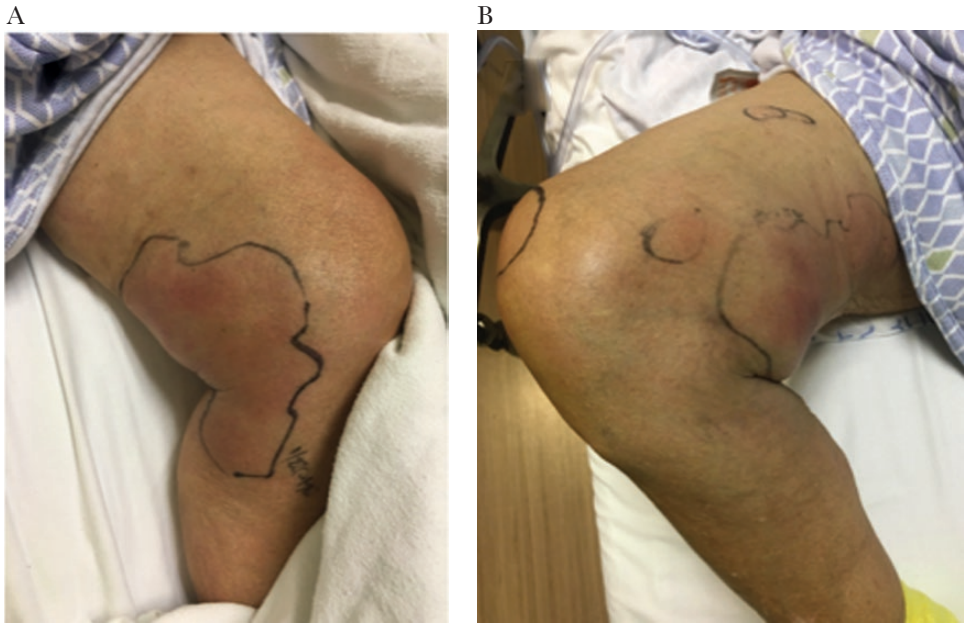

Figure 1. A, Skin lesions on left medial thigh. B, Skin lesions on right medial thigh.

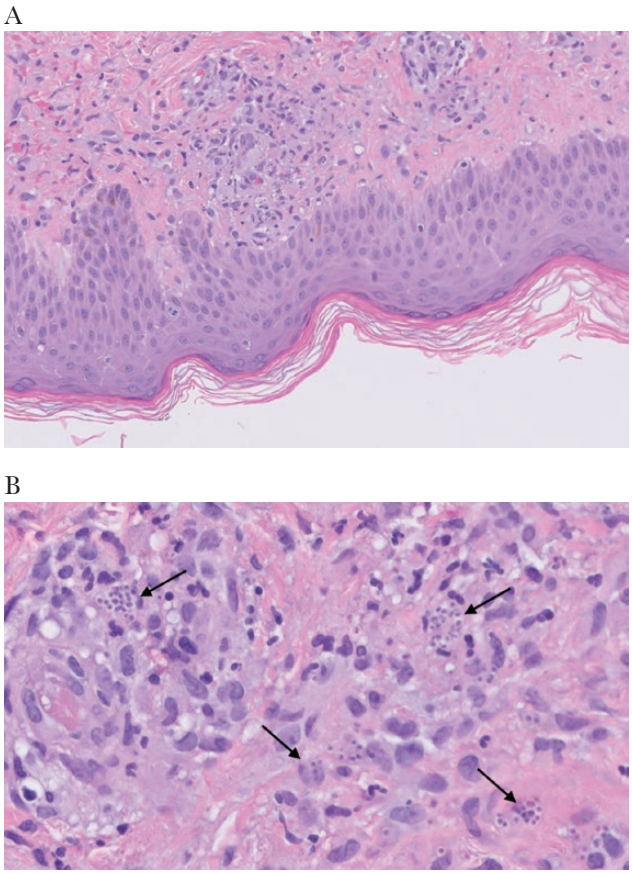

Figure 2. A, Biopsy of skin nodules, 200× magnification, hematoxylin and eosin (H&E) stain. Histologic sections show an epidermis with mild spongiosis and an underlying lymphohistiocytic infiltrate. B, Biopsy of skin nodules, 400× magnification, H&E stain. Histologic sections show numerous parasitized histiocytes (demonstrated by arrows). The organisms are circular without a well-defined capsule.

polymerase chain reaction (PCR) testing of a whole-blood sample for *T. cruzi* was also negative (performed at ARUP Laboratories). Tissue obtained from the cutaneous biopsy specimen identified *T. cruzi* by sequencing of the internal transcribed spacer 2 and D2 region of the 28S rRNA gene (performed at Stanford Health Care [1–3]).

Given the patient's remote exposure to an area endemic for *T. cruzi*, she was diagnosed with reactivation of Chagas disease (CD). Immunosuppression was weaned, and oral benznidazole 150 mg twice daily (~5 mg/kg/d) was initiated.

Concurrent with the finding of CD, the patient was also found to have disseminated cytomegalovirus (CMV) disease. Plasma CMV viral load was >1.2 million copies/mL. Lung, colon, and skin biopsies all contained cells demonstrating cytopathic changes, which were positive by CMV immunostaining. Intravenous ganciclovir was started.

With treatment, the patient's constitutional symptoms improved, and the skin lesions became less tender and erythematous. However, 1 month after the initiation of benznidazole, the patient developed *Enterobacter cloacae* bacteremia and septic shock. Shortly thereafter, she died.

Chagas Disease Epidemiology and Natural History

T. cruzi is primarily transmitted to humans via inoculation of wounds or mucosal membranes with infected feces of blood-sucking triatomine insects. CD is endemic throughout much of Latin America. However, as people have migrated from endemic areas, CD has become increasingly prevalent in traditionally nonendemic regions. In the United States, it is estimated that 1.3% of Latin American immigrants are infected with *T. cruzi* [4].

In acute CD, nearly all infected individuals have an effective host immune response that controls the parasitemia within 1–2 months of initial infection. However, in the absence of effective antiparasitic treatment, tissue infection persists for the life of the host. Chronic indeterminate CD occurs in persons without signs or symptoms of infection, with normal electrocardiogram, and normal radiographic appearance of the chest, esophagus, and colon. Indeterminate CD may persist for life or progress to determinate CD in 20%–30% of patients. Determinate CD results from tissue destruction related to persistent parasite replication and the immune response. It manifests with cardiac disease (conduction abnormalities, arrhythmias, dilated cardiomyopathy) and, less frequently, gastrointestinal disease (esophageal/colonic dysmotility and dilatation) [5, 6]. In some immunocompromised persons, chronic (indeterminate or determinate) CD can reactivate.

In conjunction with clinical symptoms, diagnosis of CD reactivation can be aided by laboratory testing. Serologic tests will be positive in most patients infected with *T. cruzi*. In chronic CD, patients can have transient parasitemia detected on microscopic examination of whole blood (or, preferably, buffy coat) smears [7]. With CD reactivation, patients often have more persistent parasitemia [8]. Positive *T. cruzi* blood PCR assays are suggestive but not diagnostic of reactivation. However, positive blood PCR results can herald the development of subsequent invasive Chagas disease reactivation in immunocompromised patients. Furthermore, rising parasite numbers demonstrated by quantitative PCR in serial specimens are highly suggestive of reactivated disease [8].

Reactivation of Chagas Disease

CD reactivation is best described in patients with advanced Chagas cardiomyopathy who undergo orthotopic heart transplantation [9–11]. The immunosuppressive drugs used to prevent transplant rejection predispose to CD reactivation. In these patients, reactivation most commonly manifests first as asymptomatic parasitemia or acute myocarditis [12]. Reactivation can also present as subcutaneous lesions [13], panniculitis [14], or, less commonly, meningoencephalitis [15]. Case series involving other solid organ transplant recipients (mostly renal transplant recipients) describe similar manifestations of CD reactivation [16–19]. CD reactivation is also known to occur in people with HIV/AIDS, most commonly presenting as meningoencephalitis [20] and/or brain abscesses (chagomas) [3, 21]. CD reactivation has also been described in patients receiving chemotherapy for hematologic and solid malignancies [22–25] and hematopoietic cell transplant (HCT) recipients [26–29].

Reactivation of Chagas Disease in Patients With Autoimmune Rheumatic Disease

There is a paucity of data regarding CD reactivation in patients receiving immunosuppressive therapy for autoimmune rheumatic diseases (ARDs; includes conditions such as systemic lupus erythematosus [SLE], rheumatoid arthritis, dermatomyositis, mixed connective tissue disease, and scleroderma). Compared with transplant recipients, patients with AIDS, and those receiving chemotherapy, patients undergoing treatment for ARD are often less immunosuppressed. However, it is unclear whether the dearth of literature in this cohort reflects infrequent reactivation or simply a lack of published case reports.

Among published English-language case reports that describe CD reactivation in patients with ARD on immunosuppressive regimens, the minority describe symptomatic CD reactivation (Table 1). Two patients developed brain chagomas—1 patient was successfully treated [30], and the other expired shortly after diagnosis [31]. Two other patients presented with Chagas skin lesions [30, 32], 1 of whom suffered recurrent disease after a course of benznidazole [30]. Other cases describe asymptomatic reactivation detected by *T. cruzi* PCR [33, 34], for which 1 patient was treated with off-label posaconazole after failing therapy with benznidazole [33]. The remaining patient reports describe possible reactivation detected through *T. cruzi* blood PCR positivity on a single test [30, 35]; given the absence of symptoms and serial testing, it is unclear if these patients had true CD reactivation or merely intermittently detectable parasites associated with chronic CD.

Although limited by small sample size and abbreviated longitudinal follow-up, other studies have attempted to investigate the risk for patients with ARD developing CD reactivation while on immunosuppression. One such study described 2 of 13 patients with ARD who developed symptomatic reactivation on immunosuppressive therapies over a 2-year period, and another 5 patients who developed possible CD reactivation detected by a single positive *T. cruzi* blood PCR test (Table 1) [30]. In other case series, the majority of immunosuppressed patients with ARD and CD were treated for chronic CD before the development of any evidence of CD reactivation, and only a small minority of these patients subsequently developed CD reactivation while receiving immunosuppression [25, 36, 37]. In 1 such study, 6 of 8 patients with ARD and CD were treated in this manner with varying regimens of benznidazole and nifurtimox. Three patients were treated for CD before a diagnosis of an ARD was made. Only 1 of the patients who received such treatment subsequently developed CD reactivation while receiving immunosuppression (further patient details not specified) [36]. In another study, 11 of 14 patients with chronic CD and ARD were treated for chronic CD with benznidazole for 60 days at the time of study enrollment, and none of the 14 patients experienced CD reactivation while receiving immunosuppression during follow-up [25]. Lastly, 3 patients with ARD and chronic CD were all treated at the time of CD diagnosis with benznidazole for 60 days; none of these patients developed subsequent CD reactivation during a 36-month follow-up

Table 1. Published Studies Describing Chagas Disease Reactivation (or Possible Reactivation) in Patients With Autoimmune Disease who Were Receiving Immunosuppressive Therapy

Study	Patient	Autoimmune Disease	Immunosuppression	Country of Origin	Chagas Diagnosis Known Before Evaluation for Reactivation	Evidence of Chagas Reactivation (or Possible Reactivation)	Treatment	Outcome
Current case	86 yo F	Limited cutaneous systemic sclerosis	Prednisone 15 mg/d, azathioprine 100 mg/d	Venezuela	No	Skin lesions—erythematous, indurated, painful nodules on medial thighs and upper extremity	Benznidazole	Patient died 1 mo after initiation of benznidazole
Kaushal et al., 2019 [31]	88 yo F	RA	MTX	Unknown	No	Brain chagoma	Benznidazole	Patient died shortly after diagnosis
German Sanchez et al., 2019 [30]	53 yo F	SLE	Prednisone 5 mg/d, MMF, CP	All patients in study from Argentina	No	Brain chagoma and *T. cruzi* blood PCR pos	Benznidazole	PCR neg
	68 yo F	Psoriatic arthritis	Prednisone 20 mg/d, HCQ, MTX		Yes	Panniculitis and *T. cruzi* blood PCR pos	Benznidazole	Relapse with recurrent skin lesions 1 y s/p treatment
7 of 13 patients with ARDs who had Chagas reactivation (or possible reactivation)	48 yo F	RA	MTX, adalimumab		Yes	Single *T. Cruz* blood PCR pos	Benznidazole	PCR neg
	66 yo M	RA	Prednisone 5 mg/d, MTX, etanercept		Yes	Single *T. Cruzi* blood PCR pos	Benznidazole	PCR neg
Treatment durations for all patients were 1–2 mo	81 yo F	RA	Prednisone 5 mg/d, HCQ, MTX, leflunomide		Yes	Single *T. Cruzi* blood PCR pos	Nifurtimox	PCR neg
	66 yo F	Sjogren syndrome	Prednisone 5 mg/d, HCQ		Yes	Single *T. Cruzi* blood PCR pos	Benznidazole	PCR neg
	57 yo F	Vasculitis	Prednisone 5 mg/d, CP		No	Single *T. cruzi* blood PCR pos	Benznidazole	PCR neg
Vacas et al., 2017 [35]	57 yo M	Psoriatic erythroderma	Infliximab	Argentina	Yes	Single *T. cruzi* blood PCR pos	Benznidazole × 45 d	PCR neg
Navarrete-Dechent et al., 2015 [34]	52 yo M	Psoriasis	Adalimumab	Chile	Yes—Chagas megacolon, received preemptive treatment with nifurtimox	*T. cruzi* blood PCR pos 8 months following preemptive nifurtimox	Repeat course nifurtimox × 2 mo	PCR neg
Burgos et al., 2012 [32]	44 yo F	SLE	Prednisone 50 mg/d, azathioprine 50 mg/d	Paraguay	No	Parasitemia, skin lesions—erythematous, painful nodules that progressed to ulcer and eschar	Benznidazole × 2 mo	Clinically improved
Pinazo et al., 2010 [33]	44 yo F	SLE	Steroids, CP	Argentina	Yes—chronic indeterminate Chagas	*T. cruzi* blood PCR pos, treated with benznidazole with recurrent PCR pos	Benznidazole × 2 mo, and then posaconazole × 3 mo for relapse	Serial PCR neg after posaconazole

Abbreviations: CP, cyclophosphamide; HCQ, hydroxychloroquine; MMF, mycophenolate mofetil; MTX, methotrexate; NA, not applicable; neg, negative; PCR, polymerase chain reaction; pos, positive; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

period [37]. Though these preliminary data are intriguing, larger population studies, conducted over longer durations, are needed in order to draw more substantial conclusions about factors predisposing to CD reactivation in this cohort and the outcomes of prophylactic therapy.

DISCUSSION

Our patient is among the few in whom symptomatic CD reactivation was documented in the setting of immunosuppressive therapy for an ARD. Our patient likely had unrecognized determinate CD, clinically manifested by tachy-brady syndrome requiring a pacemaker [38]. CD reactivated after intensification of her immunosuppression regimen, ultimately manifesting as disseminated skin nodules, with sequencing of the skin biopsy revealing *T. cruzi*.

Our patient's case was unique in that symptomatic CD reactivation occurred in the setting of a negative *T. cruzi* blood PCR. Typically, *T. cruzi* blood PCR positivity develops before symptomatic reactivation [11]. Though it is unclear why our patient's PCR was negative, it is possibly related to blood volume collected or PCR test characteristics. Importantly, this demonstrates that PCR positivity should not be the sole diagnostic measure in the evaluation for CD reactivation; assessment must also include careful clinical evaluation.

CD reactivation in patients being treated for ARD additionally involves a different degree of immunosuppression compared with other better-studied cohorts. An effective host response against *T. cruzi* requires both cellular and humoral immunity [39]. Our patient was taking low-dose prednisone and azathioprine. Corticosteroids are nonspecific immune function inhibitors [40]. However, there are no reports that describe an increased incidence of CD reactivation in patients receiving corticosteroids as their sole form of immunosuppression. Azathioprine is an antimetabolite that decreases both T and B lymphocyte production [40]. However, some heart transplant recipients with a history of Chagas cardiomyopathy preferentially receive azathioprine over mycophenolate due to a 6-fold lower incidence of CD reactivation with azathioprine compared with mycophenolate [41]. Taken together, prednisone in doses <20 mg/d and azathioprine still seem to convey a relatively low risk for CD reactivation.

In our patient's case, it is possible that more multifaceted immunosuppression led to her disease. Specifically, the synergistic effect of prednisone and azathioprine, in conjunction with her profound lymphopenia, advanced age, and uncontrolled diabetes, may have contributed to CD reactivation. However, these immunosuppressing factors still do not clearly explain our patient's profound functional immunosuppression, further exhibited by concurrent disseminated CMV disease. Based on prior data [42–45], patients with rheumatoid arthritis and SLE may have an increased risk of infection independent of immunomodulatory therapy. Further research might better delineate the relationship between CD and immune function.

Screening for Chagas Disease in Patients With ARD

Currently, consensus guidelines recommend serologic screening for CD in transplant donors and recipients with epidemiologic risk factors. A positive serologic result should be confirmed by at least 2 distinct serologic methods. In the United States, CD treatment based solely on a positive serology result in either the donor or the recipient is generally not recommended given the toxicity of the therapeutic options [46, 47]. Alternatively, transplant recipients who are seropositive should be monitored for reactivation, especially during the times of most intense immunosuppression. Laboratory monitoring employs microscopy of blood/buffy coats and blood PCR. If monitoring reveals parasitemia and/or PCR positivity (especially increasing the parasite load on serial quantitative PCRs), patients are typically given preemptive CD treatment, as the development of detectable *T. cruzi* in this cohort often heralds the development of symptomatic reactivation [46–49].

Given that data regarding CD reactivation in patients with ARD are so scant, it is uncertain if similar screening and treatment guidelines should be applied to ARD patients in the face of immunosuppression. However, in light of our patient's case and our review of the literature, our opinion is that strong consideration should be given to serologic screening for *T. cruzi* before immunosuppression for ARD in patients who have CD risk factors. (Note that serologic screening following immunosuppression may be falsely negative due to a blunted immune response.) Data are insufficient to comment on the risks versus benefits of CD treatment based solely on a positive serologic result in this cohort. However, similar to transplant recipients, for those who are seropositive, clinical assessment and serial blood microscopy/PCR monitoring should be employed during immunosuppressive therapy. There should be strong consideration of preemptive treatment of patients with parasitemia and/or PCR blood positivity (especially increasing parasite load on serial quantitative PCRs) even in the absence of symptoms; of course, evaluation/treatment for those with symptoms/signs concerning for CD reactivation. More research is needed to refine the screening and subsequent treatment approach for CD in patients with ARD.

CONCLUSIONS

This report describes CD reactivation in a patient with an ARD receiving immunosuppressive therapy. It highlights the need for more research regarding CD and reactivation in this patient population. It additionally suggests the need for broader serologic screening of patients with risk factors for CD before starting immunosuppression, and subsequent monitoring of at-risk patients while they receive such therapy.

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Patient consent. Our study does not include factors necessitating patient consent.

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