Toxoplasmic Myocarditis and Polymyositis in Patients with Acute Acquired Toxoplasmosis Diagnosed During Life

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The presence of both toxoplasmic myocarditis and myositis in the same individual has been reported only at autopsy. We report the first case of biopsy-proven toxoplasmic myocarditis and polymyositis simultaneously occurring in the same individual that was diagnosed during life. Results of her toxoplasmic serology were consistent with acute toxoplasmosis. She subsequently developed visual symptoms consistent with toxoplasmic chorioretinitis. She had a positive clinical response to therapeutic agents specific against Toxoplasma gondii. Her toxoplasmic serological profile established the diagnosis of acute toxoplasmosis. A toxoplasmic serological profile should be obtained for patients with myocarditis and/or polymyositis of unclear etiology. Endomyocardial or skeletal muscle tissue biopsies may establish the definitive diagnosis of toxoplasmic myocarditis or polymyositis, respectively. Examination of blood by polymerase chain reaction analysis before antitoxoplasmic treatment and early in the course of primary infection with T. gondii may prove useful.

Primary acute infection with Toxoplasma gondii in immunologically normal individuals is most often asymptomatic but may manifest as lymphadenopathy and/or fatigue without fever as well as myocarditis and chorioretinitis [1–3]. Infrequently, lymphadenopathy is associated with a febrile course, general malaise, headache, sore throat, and myalgia, which can rarely be followed by disseminated disease [2, 4, 5].

Myocarditis as a manifestation of acute toxoplasmosis has been reported as a rarity [6–25]. Toxoplasmic myocarditis in humans may occur clinically as an isolated disease process [12, 14, 15, 17, 18, 20–22] or as part of a variety of manifestations of the disseminated infection [7, 8, 24]. Manifestations of toxoplasmic myocarditis include arrhythmias [19], pericarditis [20, 21, 26–28], and heart failure [21, 29].

Myositis as a manifestation of acute toxoplasmosis that resembles polymyositis has also been reported as a rarity [30–48]. Dermatomyositis has been associated with toxoplasmosis [32, 37, 39], although a cause and effect relationship has not been proven.

We report the first case of clinically significant toxoplasmic myocarditis and polymyositis in a living patient. The diagnosis was established by both serology and histopathologic examination.

Case Report

Clinical History

A 43-year-old woman presented to a community hospital with cardiogenic pulmonary edema on 10 November 1994 (figure 1). She had been healthy until 8 October 1994 when she experienced a febrile illness suggestive of an upper respiratory tract infection. This illness resolved spontaneously. On 20 October 1994, she received the influenza virus vaccine; an erythematous papule was noticed at the injection site. On 23 October 1994, she developed postnasal drip, myalgias, and headache; her primary physician (R.J.) noted a single posterior cervical lymph node in addition to her symptoms and signs of a viral-like illness. On 28 October 1994, she developed severe exertional dyspnea provoked by walking 2 feet and orthopnea. Before her present illness, she could climb hills with angles of 30° to 45° for up to 2 miles with ease.

She was admitted to the hospital because of new-onset congestive heart failure (CHF). Right and left cardiac catheterizations were performed; the coronary arteries were normal, and the right heart pressures were elevated with a pulmonary capillary wedge pressure of 30 mm Hg. The ejection fraction was estimated at ~30%, and there was evidence of moderate mitral regurgitation and global hypokinesis. Endomyocardial biopsy revealed results consistent with myocarditis of unknown etiology.
Therapy with intravenous methylprednisolone (80 mg q.i.d.) and inotropic agents for presumed viral myocarditis was started. Her left ventricular function improved to the lower limits of normal. She was discharged to her home, and her medication was oral prednisone (30 mg q.d.). The corticosteroid dose was tapered over an 8-week period. At home, she initially had exertional dyspnea provoked by walking 0.2 mile that gradually resolved; by the latter part of January 1995, she could again climb up to 6 blocks of hills with minimal symptoms.

Her medical history revealed Hodgkin’s disease diagnosed in 1969 for which she was treated with radiation therapy and splenectomy. Subsequently, she underwent the following: pericardial effusion for pericardial effusion in 1979 (all cytological and microbiological diagnostic studies were unrevealing), thyroidectomy for a benign thyroid nodule in 1987, left lung resection for a benign pulmonary nodule in 1987, and resection for right scapula malignant melanoma in 1992. She developed pneumococcal sepsis and meningitis in 1993. She did not have any risk factors for HIV infection.

She ate raw beef and lamb during the second week of October 1994 in North Conway, New Hampshire. She did not have a history of raw meat ingestion or known exposure to cats. Results of toxoplasmic serology are shown in table 1.

Tapering of prednisone doses was completed on 24 January 1995. As the prednisone dose was tapered, she noticed proximal weakness of both upper and lower extremities, and physical examination revealed muscle strength of 3/5. The creatine phosphokinase level (2,915 U/L) was 15 times higher than the baseline level. The erythrocyte sedimentation rate was 35 mm/h. Biopsy of the right quadriceps muscle, which was performed on 9 February 1995 as an ambulatory procedure, showed multiple tissue cysts consistent with *T. gondii* infection.
(figure 2, upper left and upper right). An echocardiogram revealed normal size and function of the left ventricle with mild mitral regurgitation, mild tricuspid regurgitation, and an estimated ejection fraction of 60%. Treatment for toxoplasmosis (pyrimethamine, 50 mg/d [following a loading dose of 200 mg]; sulfadiazine, 6 g/d; and folinic acid, 10 mg/d) was begun. Prednisone therapy (60 mg q.d.) was reinstituted.

On 17 February 1995, she noticed progressive dyspnea and fatigue; she was admitted to a community hospital on 19 February 1995. Physical and radiological examinations revealed signs of CHF. Laboratory studies disclosed the following abnormalities: serum sodium level, 118 mmol/L; serum creatinine level, 190 μmol/L; and peripheral WBC count, 22.5 × 10^9/L. She was treated with diuretics and intravenous corticosteroids.

On February 21, 1995, she developed progressive sinus bradycardia and subsequent complete heart block associated with seizures and respiratory failure. Determination of arterial blood gas levels while the patient was receiving 60% O2 by face mask revealed the following: pH, 7.28; Pco₂, 40 mm Hg; and Pco₂, 160 mm Hg. She was resuscitated with administration of epinephrine and atropine and endotracheal intubation. Results of CT of the head and examination of CSF obtained by lumbar puncture were normal. A chest roentgenogram revealed worsening of her CHF. Her condition improved with administration of diuretics and nitrates, and she was extubated on 22 February 1995.

At the request of her primary physician, she was transferred to Stanford University Hospital (Stanford, CA) on 24 February 1995. Physical examination revealed a well-developed, thin, fatigued-appearing woman. During the examination, she was sitting up in bed without acute distress. Her blood pressure was 100/60 mm Hg; heart rate, 107; respiratory rate, 22; and temperature, 37°C. Her jugular veins were distended to the angle of her jaw. She had regular first and second heart sounds, a third heart sound, and coarse breath sounds bilaterally; deep palpation showed mild right upper quadrant tenderness without rebound tenderness or guarding.

Her liver span was 7.0; her spleen was not palpable. She was alert and oriented with respect to time, place, and person. Her cranial nerves and sensations were intact, and her muscle strength was 4+/5 bilaterally in both upper and lower extremities. Her deep tendon reflexes were 1+ throughout and symmetrical, and her toes were down going bilaterally. She had 1+ pretibial edema and 2–3+ sacral edema. Her radial, femoral, dorsalis pedis, and posterior tibialis pulses were 2+ and symmetrical.

Laboratory studies disclosed the following abnormalities: serum sodium level, 130 mmol/L; serum chloride level, 89 mmol/L; serum bicarbonate level, 28 mmol/L; blood urea nitrogen level, 11 mmol/L; serum creatinine level, 190 μmol/L; and WBC count, 19.5 × 10^9/L (81% neutrophils and 1% band forms). Her hematocrit was 31%; platelet count, 614,000/μL; serum alanine aminotransferase level, 1.38 U/mL; serum aspartate aminotransferase level, 0.71 μU/mL; serum lactate dehydrogenase level, 967 U/mL; and serum magnesium level, 0.4 mmol/L. A chest roentgenogram revealed bilateral interstitial and mild alveolar airspace changes in the right lower lobe and left retrocardiac region with small bilateral effusions. (Of note, these changes were present on her previous chest roentgenogram.)

Her diagnoses at admission were CHF, acute toxoplasmosis with skeletal muscle and presumed myocardial involvement, status post cardiac arrest, and seizures. Treatment for toxoplasmosis was continued at admission. The pyrimethamine dosage was increased to 75 mg/d. A second endomyocardial biopsy revealed the presence of multiple cysts of T. gondii. Attempts to isolate T. gondii by inoculation of specimens of theuffy coat (9 February 1995) and a peripheral blood clot (2 March 1995) into mice failed. PCR analysis of theuffy coat (9 February 1995) was negative.

By 28 February 1995, symptoms and signs of CHF were under control with diuretic administration, she was able to walk up to 100 feet without dyspnea, and her muscle strength was still 4+/5. She was discharged to her home on 1 March 1995.

On 10 May 1995, she again developed symptoms of CHF. Her medications were sulfadiazine (500 mg q.i.d.), pyrimethamine (25 mg q.d.), folinic acid (5 mg q.d.), and prednisone (5 mg q.d.). On 16 May 1995, the results of endomyocardial biopsy were consistent with active toxoplasmic myocarditis (figure 2, middle left, middle right, lower left, and lower right). Active was defined as the presence of Toxoplasma cysts surrounded by an inflammatory cell infiltrate. Her drug regimen was switched to clindamycin (600 mg q.i.d.), pyrimethamine (75 mg q.d. [following a loading dose of 100 mg]), folinic acid

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* Sabin-Feldman dye test; reciprocal of titers.

NOTE. Sera were tested in parallel in each analysis at the Toxoplasma Serology Laboratory of the Research Institute of the Palo Alto Medical Foundation (Palo Alto, CA). AC/HS = differential agglutination test; ISAGA = immunosorbent agglutination assay.
Figure 2. Upper left, stain of a right quadriceps muscle biopsy specimen from a patient with toxoplasmic myocarditis and polymyositis; the stain shows Toxoplasma cysts (arrowheads) surrounded by a moderate inflammatory cell infiltrate (stain, hematoxylin-eosin [H-E]; original magnification, ×150). Upper right, high-power magnification of upper left stain that shows necrotic skeletal muscle fibers, necrotic debris, neutrophils, histiocytes, and lymphocytes. Toxoplasma cysts are found within the inflammatory process (arrow) (stain, H-E; original magnification, ×400). Middle left, stain of a right ventricle biopsy specimen from the same patient that reveals infectious myocarditis. Toxoplasma cysts are seen within myocytes (arrowhead) (stain, H-E; original magnification, ×125). Middle right, high-power magnification of middle left stain that shows comma-shaped organisms within myocytes. A predominantly mononuclear cell infiltrate is seen around the cyst (stain, H-E; original magnification, ×400). Lower left, transmission electron micrograph of encysted bradyzoites within a myocyte from the middle left stain (original magnification, ×13,000). Lower right, high-power magnification of lower left micrograph that reveals intracystic oval-shaped organisms with double-layered pellicle (arrowhead) and an anterior placed conoid (arrow) (original magnification, ×42,000).
(10 mg q.d.), and prednisone (60 mg q.d.). She received this regimen for 1 month. Her symptoms of CHF were controlled with a therapeutic combination of lisinopril and furosemide.

On 31 July 1995, another endomyocardial biopsy was performed to determine whether she had active myocarditis; she was asymptomatic. Histopathologic examination (data not shown) did not reveal inflammation; the corticosteroid doses were tapered gradually. On 1 October 1995, prednisone therapy was discontinued. She noticed decreased vision in the right eye on 6 October 1995. Ophthalmologic evaluation showed the following visual acuities: no correction of counting fingers at 3 feet, right eye; and 20/20, left eye. Funduscopic examination disclosed recent chorioretinitis involving the right fovea. The consultant ophthalmologist believed that she had recently had toxoplasmic chorioretinitis that had been adequately treated; there were no indications for treatment of her visual symptoms at that time.

On subsequent outpatient visits, her primary physician observed that her condition had considerably improved. Lisinopril and furosemide were still being administered to control her CHF. Her last visit was on 13 August 1996.

Serological Tests
The Sabin-Feldman dye test, IgM ELISA, IgA ELISA, IgE ELISA, IgE immunosorbent agglutination assay, differential agglutination test, and agglutination test were performed as previously described [49, 50]. Serological data are shown in Table 1. The following titers were considered positive or negative, respectively, in the various tests: IgM ELISA—≥2.0, <1.7 (equivocal titers, 1.7–1.9); IgA ELISA—≥2.1, ≤1.4 (equivocal titers, 1.5–2.0); IgE ELISA—≥1.9, ≤1.4 (equivocal titers, 1.5–1.8); and IgE immunosorbent agglutination assay—≥4, ≤2.0 (equivocal titer, 3). The Sabin-Feldman dye test was considered positive at any titer; the starting dilution was 1:16.

Results of Histopathologic and Electron Microscopy Studies
Examination of the right quadriceps muscle biopsy specimen showed numerous Toxoplasma cysts surrounded by necrotic skeletal muscle fibers (Figure 2, upper left and upper right). The cysts were associated with an inflammatory infiltrate composed of neutrophils, histiocytes, lymphocytes, and pyknotic nuclear debris. Examination of the right ventricule specimens obtained by endomyocardial biopsies performed in February and May 1995 demonstrated round-to-oval Toxoplasma cysts packed with bradyzoites within the myocytes (Figure 2, middle left and middle right). A moderate inflammatory reaction of lymphocytes and histiocytes surrounded the degenerating myocytes.

Ultrastructurally, the cysts measured up to 45 μm in diameter and were enveloped by a bilayered membrane (Figure 2, lower left and lower right). The individual microorganisms averaged 4–5 μm in length and 2–3 μm in width. Elongated, polygonal, and fusiform organisms were enclosed by a double-layer pellicle. The blunted anterior aspect showed the conoid and the nucleus, and cytoplasmic organelles were displaced to the posterior end.

Discussion
The patient described above had biopsy-proven toxoplasmic myocarditis and myositis that occurred simultaneously. Results of her toxoplasmic serology were consistent with acute toxoplasmosis. It seems likely that she acquired T. gondii infection by the ingestion of contaminated raw beef or lamb. Within 2 weeks of eating raw meat, she had developed lymphadenopathy, myalgia, and headache (which are typical symptoms of clinically apparent primary toxoplasmosis). Within 4 weeks after her purported exposure to T. gondii, she developed severe myocarditis. Her condition improved with corticosteroid therapy.

Within 16 weeks from the initial alleged exposure, she developed a clinical syndrome consistent with polymyositis complicated by a relapse of her myocarditis. Both myocarditis and polymyositis resolved after she was treated with sulfadiazine and pyrimethamine and subsequently with clindamycin and pyrimethamine for T. gondii infection and after she was administered corticosteroids. She later developed visual symptoms that an ophthalmologist diagnosed as being consistent with toxoplasmic chorioretinitis; the need for further therapy was not indicated.

Inoculation of buffy coat and whole peripheral blood specimens into mice and PCR analysis of the buffy coat were negative, most likely because these tests were performed ~4 months after her purported exposure to T. gondii. It is well known that parasitemia following primary infection with T. gondii is usually of short duration [1, 52]. The probability of recovering the parasite from peripheral blood declines sharply over time [52].

It is difficult to document our patient’s immune status with certainty. She did not have any risk factors for HIV infection, and she tested negative for HIV on multiple occasions. Her immunologic parameters (including T cell function) were not evaluated further. It is not possible to determine if her history of Hodgkin’s disease, melanoma, and splenectomy were predisposing factors for the severity of her acute toxoplasmosis.

She did receive corticosteroid therapy for what was considered to be myocarditis of unknown etiology. She developed polymyositis ~1 week after tapering of the prednisone dose was completed. Whether tapering of the corticosteroid dose contributed to the development of her musculoskeletal syndrome remains unclear.

One of the striking and unusual features of this case of acute toxoplasmosis syndrome was that the patient presented with clinically apparent toxoplasmic myocarditis and polymyositis and subsequently with toxoplasmic chorioretinitis. In ~90% of otherwise immunocompetent individuals, acute toxoplasmosis is clinically silent. Symptoms, if present at all, are self-
limited and nonspecific; treatment is rarely required. The most frequently observed clinical manifestations are lymphadenopathy and fatigue without fever [49].

Although we cannot state that our patient was immunologically "normal," she did not have the usual underlying immunosuppressive conditions known to predispose to the development of severe toxoplasmosis when she had her first episode of myocarditis [53]. Splenectomy alone has not been found to be a risk factor for clinically apparent and severely symptomatic toxoplasmosis [53].

The presence of both toxoplastic myocarditis and polymyositis in the same individual has been reported only at autopsy [23–25]. Zuelzer [23] reported the case of a 9-day-old boy who was admitted to the hospital because of lack of appetite, drowsiness, and convulsions. Autopsy revealed involvement of the myocardium and psoas muscle by T. gondii accompanied by an inflammatory infiltrate. Other organs that were involved included the brain, lungs, kidneys, adrenal glands, and testicles.

Kass et al. [24] reported the case of a 60-year-old woman who presented with skin rash, arthralgias, and myalgias. Necropsy revealed T. gondii and inflammation involving the gastrocnemius, lingual, pharyngeal, temporal, sternomastoid, deltoid, pectoral, arm biceps, triceps, brachioradial, intercostal, spinal erector, greater psoas, diaphragmatic, greatest gluteal, thigh biceps, and quadriceps muscles. The parasite, without inflammatory cells, was also demonstrated in the myocardium. T. gondii was also seen in the brain. T. gondii was isolated by means of mouse inoculation studies from specimens from multiple organs, including skeletal muscle tissue. Hooper [25] reported the case of a 43-year-old man who presented with panhypopituitarism and cirrhosis of the liver. Postmortem examination revealed T. gondii and inflammation involving his myocardium and diaphragm; the brain, lungs, esophagus, retroperitoneal fat, and bone marrow were also involved.

Toxoplastic myocarditis is not a common form of myocarditis and may be difficult to diagnose [10]. The clinical manifestations of toxoplastic myocarditis are not distinctive from other causes of myocarditis [11]. In most instances, the diagnosis has been made incidentally at autopsy, when inflammatory changes in the myocardium and the identity of the parasite were found [7–10, 23–25]. It has also been diagnosed by isolation of the parasite following mouse inoculation with heart muscle specimens obtained after death and lymph node material obtained before death [24]. Before death, the diagnosis has been suspected in the presence of clinical, radiological, and electrocardiographic evidence of myocarditis and in the presence of positive toxoplastic serologies without other identifiable causes of myocarditis [12, 14, 15, 17, 18, 20–22].

The diagnosis of toxoplastic myocarditis in our patient's case was made by endomyocardial biopsy during life. In one study [54], histopathologic examination of the endomyocardial biopsy specimen was shown to be an indicator of active infection; this examination was demonstrated to be as sensitive as the prospective serology for evidence of seroconversion to T. gondii by means of the sensitive double-sandwich IgM ELISA [55] and the Sabin-Feldman dye test [56]. The initial symptoms of myocarditis in our patient abated with corticosteroid therapy. Such a response to corticosteroids has been reported by other investigators in the treatment of toxoplastic myocarditis. Cunningham [21] reported a case of pancarditis associated with acute toxoplasmosis in which the cardiac manifestations did not respond to specific antitoxoplastic therapy until prednisolone was added to the regimen.

The effectiveness of antitoxoplastic treatment for toxoplastic myocarditis has not been appropriately evaluated because of the sporadic nature of the disease. Corticosteroid therapy in addition to the antiparasitic regimen seems to be indicated at least in the presence of arrhythmias and conduction defects [11].

A cause and effect relationship between toxoplasmosis and an acute or subacute clinical syndrome resembling polymyositis or dermatomyositis has been reported [30, 31]. It has been difficult to establish T. gondii as the etiologic agent of these two syndromes. During the acute primary infection in immunocompetent individuals, T. gondii usually infects skeletal muscle as well as other tissues and organs. Thus, it is not possible to determine with absolute certainty whether polymyositis or dermatomyositis is caused by T. gondii itself or by the immune response of the host to the parasite or whether the organism is an innocent bystander.

Polymyositis and dermatomyositis associated with toxoplasmosis have been diagnosed by identifying the organism in skeletal muscle tissue [32, 35–37, 39]. Of interest, PCR analysis of muscle biopsy specimens from patients with inflammatory myopathy and increased levels of antibodies to Toxoplasma failed to demonstrate T. gondii DNA [57]. The association between these two disorders and toxoplasmosis has also been proposed because of positive toxoplastic serologies and in some instances because of a significant positive response to therapeutic agents specific against T. gondii [40–47, 58–61]. In our case, there was a clear response of symptoms of polymyositis following treatment with both antitoxoplastic drugs and corticosteroids. The fact that serological titers were not lowered following specific treatment, as observed in this case, is not unusual.

A toxoplastic serological profile can establish the diagnosis of acute toxoplasmosis [49]; this profile should be obtained for patients who present with myocarditis and/or polymyositis of unclear etiology. The diagnosis of toxoplastic myocarditis during life is difficult; at present, it relies on a compatible clinical syndrome, exclusion of other known causes, and evidence of acute toxoplastic infection by demonstration of T. gondii in accessible tissue specimens or by serological tests revealing an acute pattern [19, 49]. Endomyocardial biopsy may establish the definitive diagnosis in certain instances, like the case reported here.

The diagnosis of toxoplastic polymyositis can be made by the identification of the parasite in skeletal muscle tissue and
serological evidence of acute toxoplasmic infection. Examination of blood by PCR analysis before antitoxoplasmic treatment and early in the course of primary infection with T. gondii may prove useful. To our knowledge, this type of testing has not been done.

References

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51. deleted in proof.


