Systemic vasculitis associated with *Fasciola hepatica* infection

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We report the case of a 50-year-old man who presented with systemic vasculitis associated with *Fasciola hepatica* infection. The patient presented with severe skin, kidney, spleen, ophthalmic, and neurological compromise. An immunological examination for primary vasculitis was negative and other infections were discounted by microbiological and serological analyses. The patient was treated with steroids without clinical response. The *Fasciola hepatica* infection was confirmed by the presence of specific immunoglobulin G (IgG) serum antibodies detected by a quantitative enzyme-linked immunosorbent assay (ELISA) with an optical density (OD) of 0.483 OD units (normal value $<$ 0.170 OD units) and a high-titre complement fixation (1/80 dilution). The patient received treatment with triclabendazole and all symptoms and systemic manifestations resolved within weeks. Hence, this previously unreported vasculitis-associated infection, if identified opportunely, can be treated and cured.

The vasculitides are a heterogeneous group of uncommon diseases characterized by blood vessel inflammation and necrosis. Several factors are involved in the aetiology of the vasculitides including age, gender, major histocompability complex (MHC) genes, and environmental factors (1). Although the exact causes are unknown, some cases of the disease have occurred after bacterial, viral, or parasitic infections (2–5). In this report, we describe a case of severe multisystemic vasculitis, uniquely associated with an infection by *Fasciola hepatica*, a parasitic nematode, whose larval stage infects a large number of people in South America and in some European countries (6, 7).

Case report

A 50-year-old man with a 2-week history of cough, rhinitis, general discomfort, and intense generalized myalgia was referred for evaluation. A week before admission, he received azithromycin. Physical examination disclosed fever (38°C) and erythematous lesions of the thorax and four extremities. He was admitted to the hospital. Laboratory analyses showed a white blood cell count of 40 800 with 40% eosinophils. Erythrocyte sedimentation rate was 63 mm/h, C-reactive protein 303 mg/dL (normal range 0.1–5.0 mg/dL), alkaline phosphatase 522 U/L (normal range 38–126 U/L), aspartate amino transferase 227 U/L (normal range 21–72 U/L), oxalo-acetic amino transferase 71 U/L (normal range 17–59 U/L), gammaglutamyl transferase 41 U/L (normal range 8–78 U/L), and total bilirubin 1.41 mg/dL. Chest radiography and routine urine and blood examinations were normal. His medical history was unremarkable except for hypertension treated with Lecardipine for the past 5 years.

During hospitalisation he persisted with fever (39°C) and elbow, ankle, and metacarpalphalangeal synovitis appeared. He also presented with red eye and macroscopic haematuria, which was confirmed on urine analysis. Renal function was always normal. Skin lesions of the extremities evolved to necrotizing ulcerations (Figure 1A). Skin biopsy specimens were obtained for histopathology study. All medicines were suspended and pulse steroids were initiated with 0.5 g of methylprednisolone intravenously daily for three pulses followed by prednisone 60 mg/day orally. Despite the use of steroids, he presented acute abdominal pain. An abdominal ultrasound showed alitiasic colecystitis and a computerized tomography (CT) scan revealed splenic infarcts. Gall bladder biopsies were consistent with median vessel necrotizing vasculitis (Figure 2A, B).

He continued with intense general compromise and referred loss of vision and lower extremity paresis

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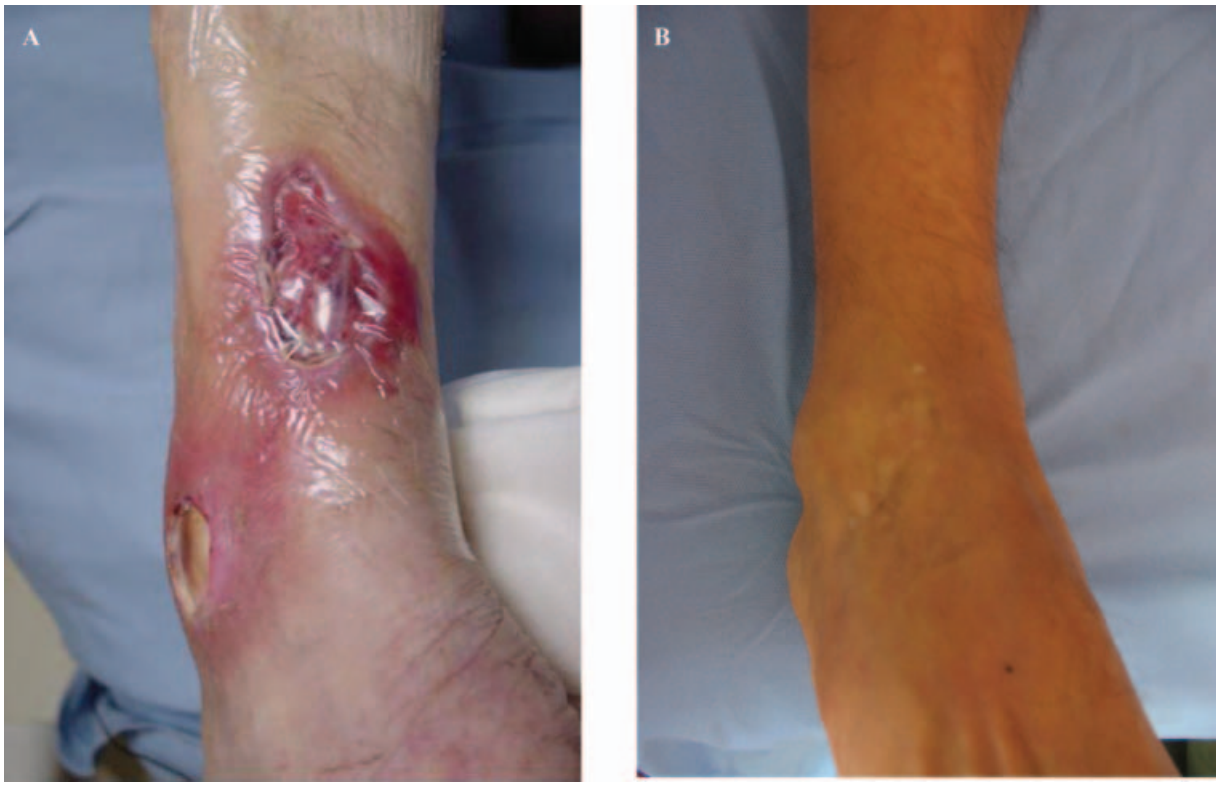

Figure 1. (A) Photograph showing active vasculitis lesions (ulcers) in right leg. (B) Same leg after treatment, lesion healed. Photographs obtained with informed consent.

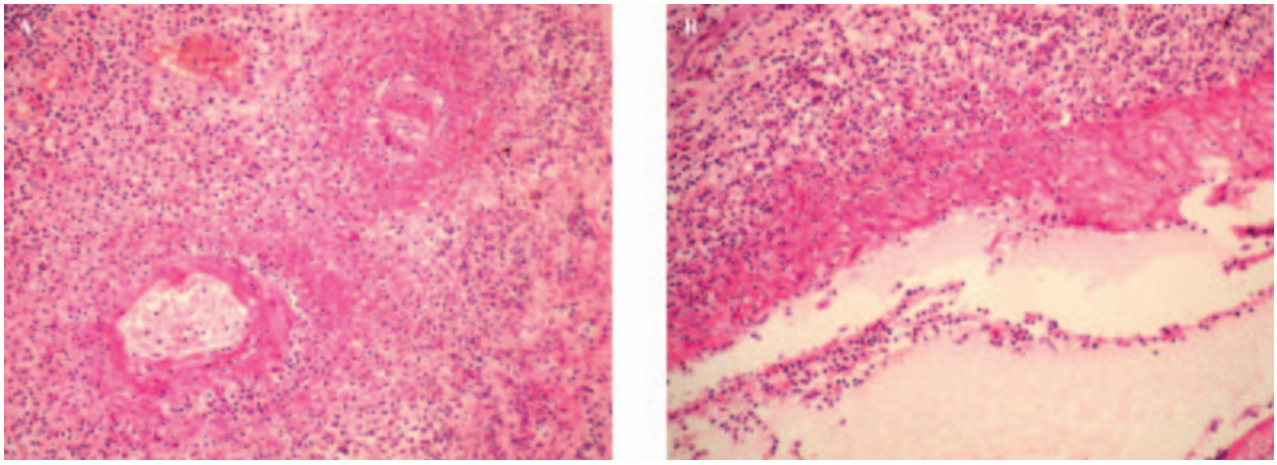

Figure 2. (A) Small-sized artery of the gall bladder affected by vasculitis with fibrinoid necrosis, inflammatory infiltrate, and associated thrombosis (upper artery). (B) Gall bladder biopsy. Detail of a medium-sized artery with fibrinoid necrosis and neutrophil predominant inflammatory infiltrate.

and paresthesias. An ophthalmological evaluation showed a bilateral retinal vasculitis with left vitritis (Figure 3A) and electrodiagnostic studies revealed mononeuritis multiplex.

Immunological analyses were negative for rheumatoid factor, cryoglobulins, anti-cardiolipin, extractable nuclear (Ro, La, Sm, RNP, Scl-70, Jo-1), anti-DNA, and anti-neutrophil cytoplasm antibodies (ANCA). Serum protein electrophoresis and total C3 and C4 complement fractions were normal. HEP-2 cell antinuclear antibodies (ANA) were positive for a 1/160 dilution and total serum IgE levels were 1482 U/mL. Serological tests for hepatitis B and C viruses, human immunodeficiency virus

(HIV), *Toxocara cannis*, and *Trichinella spiralis* were negative. Infection by *Fasciola hepatica* was confirmed by complement fixation at 1/80 dilution (cut-off value 1/5) and the presence of specific IgG serum antibodies detected by a positive quantitative enzyme-linked immunosorbent assay (ELISA) with an optical density (OD) of 0.483 OD units (normal value <0.170 OD units). The ELISA was performed using a soluble extract of somatic antigen of mature *Fasciola hepatica*, with a protein concentration of 5 μg/mL (8). A history of watercress ingestion was obtained retrospectively.

The patient started treatment with triclabendazole and began to improve. He exhibited resolution of fever, normalization of liver function, eosinophil count, and ophthalmological symptoms, with improvement of vasculitis in the ophthalmological examination (Figure 3B) and retinal angiography. He also recovered the function of his extremities and his skin ulcers healed (Figure 1B). At 24 months, follow-up *Fasciola hepatica* tests were negative (complement fixation $<1/5$ and ELISA IgG was <0.170 OD units) with no recurrence of symptoms or eosinophilia on receiving 5 mg/day of prednisone.

Discussion

Our patient had the classic features of a systemic vasculitis with evidence of skin, kidney, spleen, ophthalmic, and neurological compromise. The clinical diagnosis of vasculitis was consistent with the histological findings. The temporal association between the patient's improvement and fasciolasis supports the cause–effect relationship between these two conditions. All these findings and the clinical remission achieved only by antiparasitic treatment suggest a close relationship between the parasite and the vasculitis.

The differential diagnosis included drug-induced vasculitis (DIV), and primary vasculitis such as Churg–Strauss syndrome. The latter occurs in the setting of asthma, eosinophilia, pulmonary infiltrates, and allergic rhinitis. Our patient reported rhinitis and he had significant eosinophilia, but the clinical evolution, laboratory findings, and histology were not consistent with Churg–Strauss vasculitis. About 70% of patients with this syndrome have positive ANCA, usually p-ANCA (9), and pathological studies show intra- and extravascular granulomas rich in eosinophils, which were not found in our case (10). However, many agents have been implicated in DIV and almost every drug could potentially induce it. DIV has a wide spectrum of clinical presentations. It may be confined to the skin, or may involve other organs, ranging from a self-limiting disease to a life-threatening multi-organ vasculitis. Eosinophilia can be present in 79% of cases (11). Our patient received anti-hypertensive medication and azithromycin as an outpatient, but when he was admitted to hospital all drugs were suspended; however, the symptoms still persisted and in fact progressed.

The association between vasculitis and infections has been widely described. Viruses and bacteria are the most frequently reported agents (2, 3, 12). Even though parasites have been reported as aetiological agents of secondary vasculitis, this is an infrequent cause (2, 13). The most reported include *Strongyloides stercoralis*, *Ascaris* and *Acanthamoeba* species. *Fasciola hepatica*-induced vasculitis is a rare condition; in the English- and Spanish-language literature we did not find any other report of

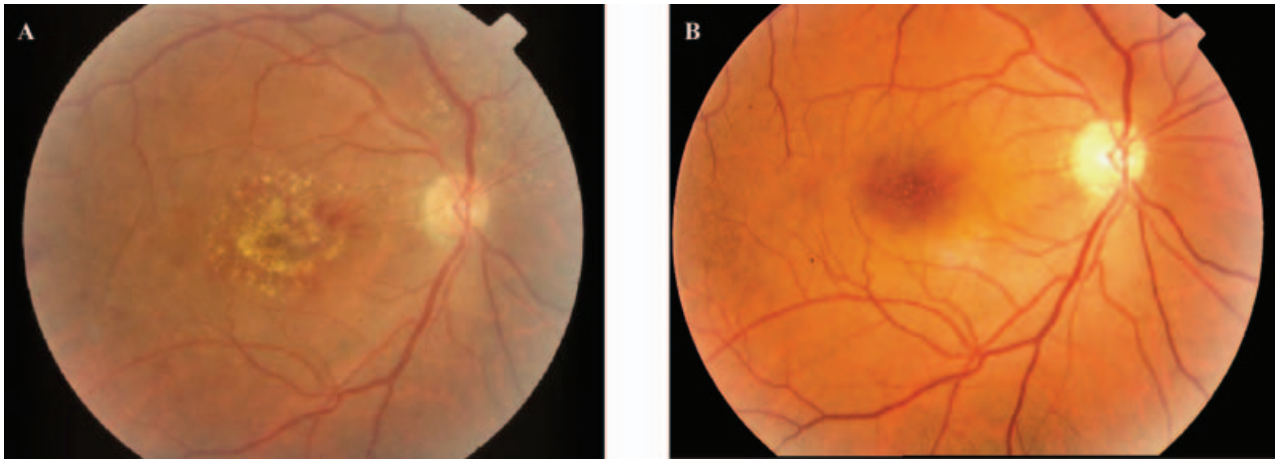

Figure 3. (A) Right eye. Small intraretinal haemorrhages, exudative macular oedema with lipid deposition (1 month after the beginning of symptoms). (B) Right eye. Complete resolution of haemorrhages and exudative macular oedema. Residual mild pigmentary changes in the macular region and some optic nerve pallor (1 year after therapy). Photographs obtained with informed consent.

fasciolasis associated with systemic vasculitis. The clinical manifestations are assumed to result from immune complex-mediated processes initiated by antigenic products derived from the agent during the invasive period (2).

The acute or invasive stage begins a few days after the ingestion of metacercariae. Symptoms, including fever, headache, and urticaria, occur in the majority of patients. After ingestion, metacercariae actively migrate across the small intestine to the peritoneal cavity, where they penetrate the liver capsule within days. The larvae maturate in the liver for 2–4 months until they reach the large bile ducts and the resting adult stage; in this phase the symptoms are usually due to bile duct obstruction (14). The period between the watercress ingestion and the beginning of the manifestations and the symptoms referred by the patient when he first consulted are concordant with those described in the literature for the acute phase. This explains why we did not find the larvae in the bile ducts or stool samples at this stage of disease. We report an uncommon clinical presentation that shows the gravity that this condition may achieve. The multisystemic involvement may be life-threatening if it is not opportunely recognized and treated.

In brief, we document a unique case of systemic vasculitis associated with fasciolasis, extending the spectrum of infectious agents associated with vasculitis. Considering the fact that infections are treatable conditions, this observation is relevant within the context of a treatment that could stop disease progression and patients' sequelae.

Informed consent of the patient was obtained for this publication.

References

1. Gonzalez-Gay M, García P. Epidemiology of the vasculitides. Rheum Dis Clin North Am 2001;27:729–49.
2. Somer T, Finegold S. Vasculitides associated with infections, immunization and antimicrobial drugs. Clin Infect Dis 1995;20:1010–36.
3. Gerber O, Roque C, Coyle P. Vasculitis owing to infection. Neurol Clin 1997;15:903–25.
4. Hamidou M, Fradet G, Kadi A, Robin A, Moreau A, Magnaval J. Systemic vasculitis with lymphocytic temporal arteritis and *Toxocara canis* infection. Arch Int Med 2002;162:1521–4.
5. Narvaez J, Biosca M, Perez-Vega C, Vilaseca-Momplet J. Fulminant systemic vasculitis in a patient with untreated asymptomatic chronic hepatitis C infection. Scand J Rheumatol 2003;32:374–5.
6. Atias A. Parasitología médica. Santiago: Editorial Mediterráneo, 1999.
7. Chester P, Clifton R, Wayne E. Medical parasitology. Barcelona: Salvat, 1986.
8. Apt W, Aguilera X, Vega F, Miranda C, Zulantay I, Perez C, et al. Treatment of human chronic fasciolasis with triclabendazole: drug efficacy and serologic response. Am J Trop Med Hyg 1995;52:532–5.
9. Jennette C, Falk R. Small-vessel vasculitis. N Engl J Med 1997;337:1512–23.
10. Klippel J, Crofford L, Stone J, Weyand C, editors. Primer on the rheumatic diseases. Atlanta, Georgia: Arthritis Foundation, 2001.
11. Merkel PA. Drug-induced vasculitis. Rheum Dis Clin North Am 2001;27:849–62.
12. Naides S. Known infectious causes of vasculitis in man. Cleve Clin J Med 2002;69 Suppl 2:SII15–19.
13. Oujamaa L, Sibon I, Vital A, Menegon P. Cerebral vasculitis secondary to *Toxocara canis* and *Fasciola hepatica* co-infestation. Rev Neurol (Paris) 2003;159:447–50.
14. Lee N, McNeely W, Shepard J, Ebeling S, Ellender S, Peters C. 50-year-old man with eosinophilia and fluctuating hepatic lesions. N Engl J Med 2002;346:1232–39.