Whipple's disease with constrictive pericarditis: A rare disease with a rare presentation

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Whipple's disease is a multisystem disease that can affect the heart with predominantly endocardial and pericardial involvement and, less often, myocardial inflammation. Previously diagnosed at autopsy, cardiac involvement in Whipple's disease is being recognized clinically more often. A 58-year-old man with Whipple's-related constrictive pericarditis, arthralgias and lymphadenopathy is described. He underwent antibiotic treatment and pericardiectomy with improvement in his clinical state.

Key Words: Constrictive pericarditis; Jejunal biopsy; Lymphadenopathy; Pericardiectomy; Whipple's disease

Whipple's disease, a rare systemic illness caused by *Tropheryma whippelii*, affects multiple organ systems, although cardiac involvement is rarely the primary presentation (1). We describe a 58-year-old man with constrictive pericarditis due to Whipple's disease in the absence of clinical valvular or myocardial involvement.

CASE PRESENTATION

The patient was clinically well until nine months before presentation, during which time he developed fatigue, exertional dyspnea, abdominal pain, bilateral leg swelling and a 13 kg weight loss. Computed tomography (CT) at a community hospital revealed mediastinal, mesenteric and retroperitoneal lymphadenopathy that was initially thought to be due to lymphoma. It was not possible to perform a diagnostic open inguinal lymph node biopsy because the patient could not lie supine due to severe orthopnea.

He was referred to The Ottawa Hospital in Ottawa, Ontario for further evaluation. On presentation, he had dyspnea, orthopnea, ascites and a 25 kg weight loss. He described a two-year history of large joint arthralgias (knees and ankles). He had no diarrhea. His physical examination revealed that he was afebrile with small axillary and inguinal lymph node enlargement. He had an elevated jugular venous pressure of 10 cm above the sternal angle, and had a positive Kussmaul's sign, ascites and bilateral leg edema. His chest x-ray showed right-sided pleural effusion and his electrocardiogram was normal.

Laboratory studies revealed hypochromic anemia with hemoglobin at 100 g/L, hematocrit at 31.8%, normal white blood cell count ($9 \times 10^9/L$) with lymphopenia ($0.6 \times 10^9/L$), and hypoalbuminemia (25 g/L) with normal immunoglobulins and serum creatinine

Maladie de Whipple et péricardite constrictive : Maladie et tableau clinique rares

La maladie de Whipple est une affection plurisystémique qui peut affecter le cœur, plus particulièrement, l'endocarde et le péricarde, et plus rarement, elle cause une inflammation du myocarde. Autrefois diagnostiquée à l'autopsie, l'atteinte cardiaque associée à la maladie de Whipple s'observe désormais plus souvent en clinique. On décrit ici le cas d'un homme de 58 ans présentant une péricardite, des arthralgies et une lymphadénopathie associées à la maladie de Whipple. Il a été traité par antibiothérapie et péricardectomie et son état clinique s'est amélioré.

(56 $\mu\text{mol/L}$). Liver enzymes showed elevated alkaline phosphatase (334 U/L) and gamma-glutamyl transferase (63 U/L), with a normal transaminase, lactate dehydrogenase and coagulation profile. Abdominal paracentesis revealed cloudy fluid with monocytic pleocytosis (58% of $1.770 \times 10^9/L$ white blood cells). Thoracentesis revealed a transudate. Peritoneal and pleural fluid cultures were negative for mycobacteria and fungi.

CT of the chest demonstrated significant mediastinal lymphadenopathy with right-sided pleural effusion and mild pericardial thickening with few foci of calcification. Abdominal CT showed congestive hepatomegaly with prominent inferior vena cava and hepatic veins, mural and mucosal fold-thickening in the jejunum and increased folds in the distal ileal loops (Figure 1A). There was associated mesenteric and retroperitoneal lymphadenopathy (Figure 1B) and bilateral sacroiliitis.

Upper endoscopy with push enteroscopy revealed nodular gastric mucosa and scalloped jejunal mucosa with flattened villi. Immunoglobulin A anti-tissue transglutaminase antibodies were negative. Tissue biopsies of both gastric and jejunal mucosa revealed high numbers of periodic acid-Schiff stain (PAS)-positive foamy histiocytes with vacuolated cytoplasm within the lamina propria (Figure 2). Acid-fast staining was negative. The patient was diagnosed with Whipple's disease.

Magnetic resonance imaging confirmed the presence of a thickened pericardium. Echocardiography and right heart catheterization demonstrated findings consistent with constriction physiology. There were no significant valvular abnormalities.

The patient was treated with ceftriaxone for 14 days and was discharged home on trimethoprim-sulfamethoxazole. The patient

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Figure 1) Computed tomography of the abdomen showing thickened prominent small intestinal mucosal folds (A; black arrows) that were consistent with Whipple's disease, with multiple enlarged low attenuation (specific for periodic acid-Schiff stain-positivity) mesenteric lymphadenopathy (B; black arrows) and ascites (white arrows in A and B)

regained weight (13 kg) during the next five months with symptomatic improvement. However, he had persistent dyspnea and ascites with ongoing clinical evidence of pericardial constriction.

The patient underwent pericardiectomy after five months of therapy. Dense fibrous adhesions were found against the right ventricular and inferior walls, which were resected fully. The pathology revealed fibrous pericardial thickening with neovascularization and focal dystrophic calcification. There were small numbers of PAS-positive macrophages (Figure 3A). CD68 immunostaining showed high numbers of macrophages throughout the pericardium. Following a lengthy search, electron microscopy revealed rare bacilliform intracytoplasmic structures (Figure 3B). These findings were consistent with resolution of the pericardial involvement of Whipple's disease.

Following pericardiectomy, the patient made a good clinical and functional recovery with near complete resolution of ascites, leg swelling and weight loss.

DISCUSSION

In 1907, George Hoyt Whipple coined the term 'intestinal lipodystrophy' (2), for what is known today as Whipple's disease. Whipple's disease has a variety of presentations, but usually includes diarrhea, weight loss, abdominal pain and arthralgias. However, one-quarter of patients have no gastrointestinal symptoms (1).

In 1952, Upton first reported cardiac involvement as a component of Whipple's disease (2). Cardiac involvement in Whipple's disease is common and usually presents with valvular or endocardial pathology or, rarely, congestive heart failure (2). All three layers of the heart may be

Figure 2) A The endoscopic biopsy of the jejunum demonstrating villi with lamina propria full of macrophages. Lymphatic dilation was also prominent (hematoxylin and eosin stain; original magnification $\times 100$). **B** The macrophages stain positive with periodic acid-Schiff stain characteristic of Whipple's disease (original magnification $\times 200$)

involved (1), with pancarditis seen at autopsy in two-thirds of the cases reported in one series (3). In 1975, McAllister and Fenoglio (2) presented a series of 19 male Whipple's disease patients. They found that 58% had clinical cardiac findings and 79% had gross cardiac lesions at autopsy, with adhesive pericarditis in 79%, fibrosis and deformity of one cardiac valve (mostly involving the mitral valve) in 53% and myocardial fibrosis in only 11% of the patients. The clinical findings included pansystolic murmurs, pericardial rub, electrocardiogram changes and congenital heart failure. Electron microscopy revealed extracellular rod-shaped bodies scattered throughout the cardiac valves and myocardium. PAS-positive macrophages were found in all cardiac specimens (2).

It is very rare that constrictive pericarditis is the primary or sole presentation of Whipple's disease. To our knowledge, there are only five reported cases of Whipple's disease associated with constrictive pericarditis. None of these cases reported constrictive pericarditis as the presenting feature. In 1978, Viletstra et al (3) reported a case of Whipple's disease diagnosed on small bowel biopsy, which had complete regression of joint and bowel symptoms with tetracycline, and then developed constrictive pericarditis with incapacitating congestive heart failure seven years later. Gastrointestinal symptoms led to the diagnosis of Whipple's disease in another patient, in whom pleuropericarditis symptoms (no biopsy was performed to confirm) predated the diagnosis by four years (2). In 1983, Crake et al (4) reported a patient with profuse lower gastrointestinal bleeding two months following pericardiectomy. The patient

was diagnosed with Whipple's disease by mesenteric lymph node biopsy and confirmed by jejunal biopsy. In retrospect, small amounts of PAS-positive material were identified in the pericardium. In 1990, Freychet et al (5) described a patient presenting with longstanding arthropathy and diarrhea with a negative jejunal biopsy, followed by development of pericardial constriction with localized myocardial involvement, diagnosed by electron microscopy of the pericardium. Finally, in 1999, Elkins et al (1) reported a man with Whipple's valvular endocarditis and pericardial involvement that was diagnosed by histology and polymerase chain reaction (PCR) of tissue. The patient presented with a left-sided stroke and deep vein thrombosis despite being on oral anticoagulation. With the exception of one case (1), the diagnosis of Whipple's disease has been established by microscopy without the use of PCR. In two cases (3,5), electron microscopy identified bacilliform rods. PCR testing for *T. whipplei* is available in few centres around the world, but in the presence of typical clinical, histological and electron microscopic findings, it is not a requirement for definitive diagnosis.

Our patient presented with pericardial constriction and no other clinical cardiac manifestation. He had no diarrhea, but had PAS-positive macrophages in his intestinal wall and pericardium, with few intracellular rod-shaped bodies, which was consistent with 'Whipple's bacteria' seen in the fibrosed pericardium on electron microscopy (Figure 3B). The pericardiectomy was performed after medical treatment. The small number of macrophages and rare bacilli likely reflect some clearing of bacteria by the medical treatment.

There is no direct relationship between the extent of cardiac involvement, and the severity and duration of the systemic disease (2). The complications of cardiac involvement in Whipple's disease are potentially fatal, warranting early detection and treatment.

The treatment of Whipple's constrictive pericarditis involves pericardiectomy (3-5) and antibiotics to eradicate *T. whipplei*. Presently, the therapeutic experience related to Whipple's pericarditis has not been published.

Could Whipple's pericarditis, like tuberculous pericardial disease, progress to constriction despite successful medical therapy? Although our patient presented with constriction, one wonders if corticosteroids could be a reasonable therapeutic adjunct to antibiotics in patients with Whipple's pericarditis without constriction, who do not achieve complete resolution of their symptoms. Future studies might address this question.

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Figure 3) A The pericardium shows dense fibrosis and scattered periodic acid-Schiff stain-positive macrophages (original magnification $\times 400$). B Electron microscopy showing rare macrophage cells containing a cross-section of bacilli (arrow) in the cytoplasm. Collagen fibres (C) surround the cell (original magnification $\times 5000$)