Ha Francis (Orcid ID: 0000-0003-3206-5725)

Refractory Seronegative Arthropathy: Think outside the Joint

Francis J. Ha[1,2] MBBS(Hons) BMedSc

Wendy Stevens[2,3] MBBS

Jonathon Darby[3,4] MBBS(Hons)

Raymond Martyres[3,5] MBBS MMed

Andrew T Burns[1,3] MBBS(Hons) BMedSc MD

1. Department of Cardiology, St Vincent's Hospital Melbourne
2. Department of Rheumatology, St Vincent's Hospital Melbourne
3. University of Melbourne, Victoria
4. Department of Infectious Diseases, St Vincent's Hospital Melbourne
5. Department of Medicine, Royal Melbourne Hospital, Melbourne

Corresponding Author: Dr Francis J. Ha

Email: francis.j.ha@gmail.com

St Vincent's Hospital Melbourne

41 Victoria Parade, Fitzroy, Victoria, 3065

Telephone: +61 03 9231 3000

Conflicts of interest: the authors report no relevant conflicts of interest

Key words: Whipple's disease, tricuspid regurgitation, Jarisch-Herxheimer reaction, rheumatoid arthritis

Word count: 500

A 67 year old male was referred to a tertiary hospital for investigation of bilateral lower limb arthralgia, peripheral oedema and weight loss. At time of referral, his symptoms had been present for 12 years with arthralgias affecting both ankles and knees with morning stiffness. He described episodic fevers, night sweats and 12kg weight loss without localising infective symptoms. He had been diagnosed with seronegative rheumatoid arthritis six years prior to this referral. Previous treatments included prednisolone, hydroxychloroquine, methotrexate, leflunomide, tocilizumab and adalimumab. These medications had been ceased prior due to lack of symptomatic benefit.

Other medical history included atrial fibrillation and pericardial calcification detected four years prior on computed tomography (CT) chest/abdomen/pelvis requested for undifferentiated weight loss. Transthoracic echocardiogram showed severe tricuspid regurgitation (TR) and moderate right ventricular dilatation (**Figure 1a and 1b**). Simultaneous right and left heart catheterisation revealed normal coronary arteries and mean pulmonary artery pressure of 21mmHg. Despite pericardial calcification (**Figure 1c**), there was no pericardial constriction.

Blood tests at referral revealed a microcytic anaemia (Hb 93g/L, MCV 80) with iron deficiency, raised inflammatory markers (CRP 78mg/L, ESR 79mm/hr) and albumin 29g/L. Autoimmune screen was unremarkable including negative rheumatoid factor, anti-cyclic citrullinated peptide and antinuclear antibody. Right foot/ankle magnetic resonance imaging showed osteoarthritic changes in midfoot joints.

Gastroscopy performed to investigate iron-deficiency anaemia showed mild gastritis and duodenitis. Duodenal biopsy revealed foamy macrophages in the lamina propria and submucosa which stained periodic acid-Schiff positive and were diastase resistant (**Figure 1d**). This was consistent with a diagnosis of Whipple's disease and confirmed with *Tropheryma whipplei* detected by polymerase chain reaction on formalin fixed tissue shavings.

The patient was commenced on intravenous ceftriaxone 2grams daily. Twelve hours after first antibiotic dose, he became febrile, tachycardic and hypotensive. He was transferred to the intensive care unit for two days of vasopressor support and administered hydrocortisone 100mg intravenously, followed by oral prednisolone 50mg daily for 3 days. After achieving haemodynamic stability, prednisolone was weaned to 15mg over 4 weeks. He was discharged on daily intravenous ceftriaxone for a total of five weeks and de-escalated to oral

trimethoprim-sulfamethoxazole 160/800mg twice daily for a planned 12 months. Six weeks after antibiotic commencement, his arthralgias improved, inflammatory markers normalised (CRP 4mg/L, ESR 9mm/hr) and he had gained 10kg. The patient will be closely observed to determine whether tricuspid valve replacement may be required for refractory right heart failure from residual TR.

Whipple's disease is a rare infectious disease caused by gram-positive bacillus *Tropheryma whipplei*. Diagnosis is often delayed due to multisystem features including arthralgias, diarrhoea and weight loss(1). This patient's TR and pericardial calcification likely reflects longstanding cardiac involvement of infection(2, 3). Upon antibiotic therapy, patients may rarely develop a Jarisch-Herxheimer reaction as reflected in this patient, with one previous reported case(4). Significant pre-treatment with immunosuppression including several biologic agents likely increased the risk of such an immune reaction. Despite its rarity, clinical suspicion for Whipple's disease should be raised in patients with seronegative arthritis unresponsive to multiple immunosuppressive therapies, particularly with unexplained valvular and pericardial calcification.

References

1. Lagier JC, Lepidi H, Raoult D, Fenollar F. Systemic Tropheryma whipplei: clinical presentation of 142 patients with infections diagnosed or confirmed in a reference center. Medicine (Baltimore). 2010;89(5):337-45.

2. Lepidi H, Fenollar F, Dumler JS, Gauduchon V, Chalabreysse L, Bammert A, et al. Cardiac valves in patients with Whipple endocarditis: microbiological, molecular, quantitative histologic, and immunohistochemical studies of 5 patients. The Journal of infectious diseases. 2004;190(5):935-45.

3. Keane MG, Shariff M, Akbhar A, Trembling P, Cohen P, Smith G. Asymptomatic pericardial calcification in Whipple's disease. J R Soc Med. 2009;102(11):489-90.

4. Playford RJ, Schulenburg E, Herrington CS, Hodgson HJ. Whipple's disease complicated by a retinal Jarisch-Herxheimer reaction: a case report. Gut. 1992;33(1):132.

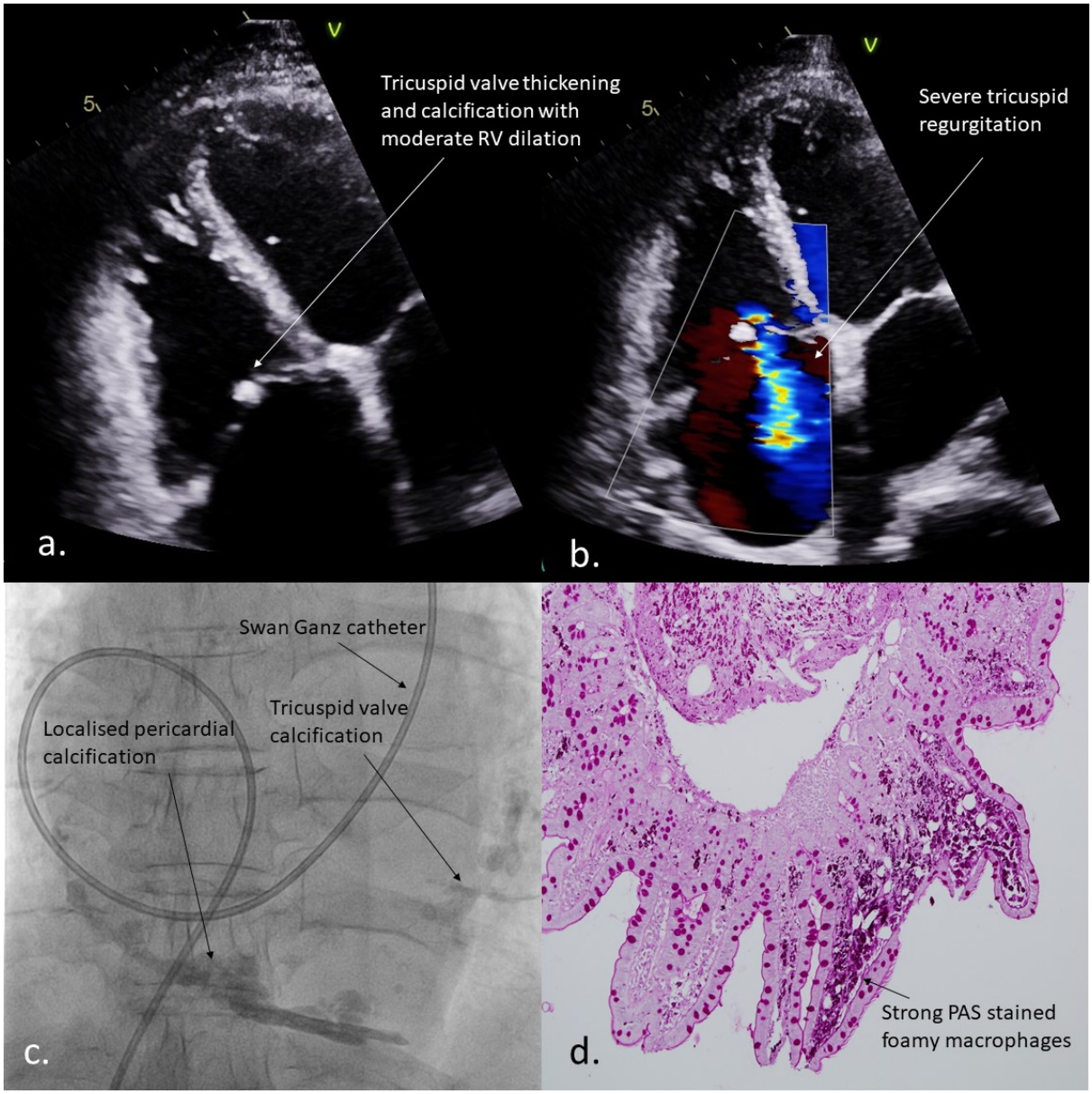
Figure 1.

a. Apical four chamber transthoracic echocardiogram showing right ventricular dilation and focal tricuspid valve calcification.

b. Apical four chamber transthoracic echocardiogram with colour flow Doppler showing severe tricuspid regurgitation.

c. Fluoroscopy during right heart catheterization using a Swan Ganz catheter showing pericardial and tricuspid valve calcification.

d. Periodic acid–Schiff stain of duodenal biopsy showing strongly positive staining of foamy macrophages in mucosa and submucosa.



Brief Abstract

Whipple's disease is a rare infectious disease caused by gram-positive bacillus Tropheryma whipplei. Diagnosis is often delayed due to multisystem features including arthralgias, diarrhoea and weight loss. We report a case of a 67 year old male referred to a tertiary hospital for further investigation of longstanding seronegative arthritis and isolated tricuspid regurgitation. A subsequent biopsy performed during gastroscopy for iron-deficiency anaemia was consistent with a diagnosis of Whipple's disease. The patient was treated with intravenous antibiotics and developed a Jarisch-Herxheimer reaction acutely. He was managed supportively, and after three months of antibiotics, his arthralgias improved and inflammatory markers normalised. Despite its rarity, clinical suspicion for Whipple's disease should be raised in patients with seronegative arthritis unresponsive to multiple immunosuppressive therapies, particularly with unexplained valvular pathology.

Refractory Seronegative Arthropathy: Think outside the Joint

Francis J. Ha[1,2] MBBS(Hons) BMedSc

Wendy Stevens[2,3] MBBS

Jonathon Darby[3,4] MBBS(Hons)

Raymond Martyres[3,5] MBBS MMed

Andrew T Burns[1,3] MBBS(Hons) BMedSc MD

1. Department of Cardiology, St Vincent's Hospital Melbourne
2. Department of Rheumatology, St Vincent's Hospital Melbourne
3. University of Melbourne, Victoria
4. Department of Infectious Diseases, St Vincent's Hospital Melbourne
5. Department of Medicine, Royal Melbourne Hospital, Melbourne

Corresponding Author: Dr Francis J. Ha

Email: francis.j.ha@gmail.com

St Vincent's Hospital Melbourne

41 Victoria Parade, Fitzroy, Victoria, 3065

Telephone: +61 03 9231 3000

Conflicts of interest: the authors report no relevant conflicts of interest

Key words: Whipple's disease, tricuspid regurgitation, Jarisch-Herxheimer reaction, rheumatoid arthritis

Word count: 500