CASE REPORT

Whipple's endocarditis presenting as ulnar artery aneurysm; if you don't look, you won't find

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SUMMARY

A 54-year-old female patient presented to her local district general hospital with a painful, swollen left arm. Imaging revealed an ulnar artery aneurysm. The aetiology was embolic, with an echocardiogram revealing vegetations on the aortic valve. The patient was treated empirically for 6 weeks with amoxicillin and gentamicin for endocarditis. Eight months later, she had an elective aortic valve replacement for symptomatic aortic regurgitation. The valve was culture negative but analysis by 16S rDNA PCR was positive for *Tropheryma whippelii*. In retrospect, the ulnar artery aneurysm and a history of arthralgia were attributed to an underlying diagnosis of Whipple's endocarditis. She continues on antibiotic treatment with resolution of her arthralgia and no clinical signs of infection. Once thought to be rare entity, molecular assays have revolutionised the diagnosis of Whipple's endocarditis, but this case highlights the difficulties and pitfalls in diagnosis.

BACKGROUND

Tropheryma whippelii is the causative agent of Whipple's disease, a rare chronic multisystemic condition classically presenting with diarrhoea, weight loss and malabsorption, with a reported prevalence of 1:1 000 000.¹ The clinical disease was first described in 1907² although the causative organism was not described until 1992.^{3–4} Cardiovascular disease is present in up to one-third of patients with Whipple's and may present as pericarditis, congestive heart failure or culture-negative endocarditis, usually affecting the aortic or mitral valve.^{5,6}

Whipple's disease is probably underdiagnosed as the organism does not grow on standard culture and molecular testing, which is the gold standard, requires an index of suspicion. Additionally, it is only performed in reference laboratories. Classical features of endocarditis present in the Duke criteria⁷ such as fever and a history of valvulopathy are often absent in Whipple's endocarditis. The mainstay in the diagnosis is histological and molecular analyses, but these are not always performed, and require explanted valvular tissue.

In this case report, we describe a patient with a long history of arthralgia and an acute episode of embolic phenomena secondary to endocarditis caused by *T. whippelii*. Our patient did not fit the classic demographic of Whipple's disease, which has a strong male preponderance,⁸ but did have clinical clues including arthralgia (present in up to 75% of cases of endocarditis due to *T. whippelii*)⁹

which can precede the diagnosis of Whipple's by 6–8 years.^{5,10} She did not appear to have any gastrointestinal involvement of her Whipple's disease which is in keeping with cases from the literature.^{5,6}

This case highlights that the male preponderance of this disease should not exclude investigation of blood culture-negative infective endocarditis (BCNE) in women, that the diagnosis is very difficult presurgery, and the importance of fully investigating by histological and molecular methods of excised valvular tissue in cases of culture-negative endocarditis. The outcome for our patient if molecular analysis had not been performed was likely to have been recurrence, which is associated with exceedingly poor outcomes.

CASE PRESENTATION

A 54-year-old woman was referred by her general practitioner to the vascular department of a district general hospital with a sudden onset, atraumatic, painful swelling of her left arm. On examination, the left arm was swollen distally to mid-elbow, with an impalpable ulnar pulse at the wrist. There was no cellulitis or break in the skin. There was no evidence of compartment syndrome and no neurological deficit.

She had an ultrasound scan which demonstrated an ulnar artery pseudoaneurysm with associated haematoma (figure 1). The vascular team were mindful of a possible embolic phenomenon and started her on intravenous amoxicillin (2g every 4 hours) and gentamicin (1 mg/kg every 12 hours) for native valve endocarditis with an indolent presentation, as per BSAC (British Society for Antimicrobial Chemotherapy) guidelines¹¹ while arranging an echocardiogram. Cardiac examination was documented as normal, with no evidence of cardiac failure or other peripheral stigmata of infective endocarditis. Three sets of blood cultures were taken preantibiotics and were negative. Her inflammatory markers showed only a small rise in C-reactive protein at 22 mg/L. She reported no systemic symptoms other than occasional night sweats which she had attributed to the menopause. Her prior medical history was unremarkable apart from a consultation with a rheumatologist regarding arthralgia of the shoulders and wrists which was attributed to osteoarthritis.

She required open repair of the ulnar artery and fasciotomy of the left forearm after a failure to respond clinically to intravenous antibiotics. No samples were sent from the operation for either microbiology or histology. Her echocardiogram

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Figure 1 Doppler ultrasound left arm demonstrating an ulnar artery aneurysm.

demonstrated a dysmorphic thickened aortic valve allowing aortic regurgitation, with two small mobile echo dense masses considered likely to be vegetations (Video 1).

Video 1 Echocardiogram demonstrating a restricted and thickened aortic valve with two small areas suggestive of vegetations

She was treated for 6 weeks with amoxicillin and gentamicin. During this time, her C-reactive protein declined to 2 mg/L. No microbiological investigations for culture-negative endocarditis were performed at the time. A repeat transthoracic echocardiogram at the completion of her antibiotics showed improvement in the size of the echo dense masses, but without resolution, and ongoing aortic regurgitation.

She was monitored as an outpatient and her inflammatory markers remained low. Over a 6-month period, she began to report exertional dyspnoea on inclines and stairs at NYHA (New York Heart Association) class II with no accompanying chest discomfort, dizziness or syncope. There were no symptoms to suggest any further embolic phenomena elsewhere. A post-treatment transthoracic echocardiogram demonstrated moderate to severe aortic regurgitation and a trileaflet valve with mild degree of stenosis. Mild mitral and mild tricuspid regurgitation was noted with preserved left ventricular thickness and function. Coronary angiography demonstrated no significant coronary disease in a right dominant coronary circulation. With these findings, she was referred for an aortic valve replacement to our tertiary cardiothoracic centre. The operative findings were of thickened aortic valve leaflets, with no obvious mobile mass associated. She had a metallic St Jude valve sited with a satisfactory intraoperative outcome. Her postoperative course was unremarkable and she was discharged from hospital after 7 days.

Her valve was sent for microscopy and culture and demonstrated no growth after 5 days of incubation. No specimen was sent to histopathology. Noting the history of a culture-negative endocarditis the microbiology department requested the valve be sent for 16S PCR analysis. This was positive for *T. whipplei*.

TREATMENT

Following the aortic valve replacement, the patient was discharged feeling well, and off antibiotics. She was recalled to the Infectious Diseases clinic following the positive 16S PCR result. Blood was sent for analysis for *T. whipplei* by 16S PCR and was negative. Serology is not available within the UK currently outside of a research setting. The patient was commenced on oral trimethoprim-sulfamethoxazole at a dose of 960 mg twice daily.

OUTCOME AND FOLLOW-UP

At follow-up 6 months later she was well, and haematological and biochemical parameters were within normal limits. She had some residual shortness of breath but was able to climb a flight of stairs and her exercise tolerance was over a mile. ECG showed sinus rhythm at 72 bpm and echocardiogram showed a well-seated aortic valve replacement with an ejection fraction of 50%–55% with mild transvalvular aortic regurgitation.

Treatment is planned for a minimum duration of 1 year on the basis of the published literature (see the Discussion section).

DISCUSSION

Whipple's disease and endocarditis

The incidence of Whipple's disease is highly variable and likely related to different rates of testing in different regions.⁸ A high prevalence of Whipple's disease has been reported in parts of France, Switzerland and Germany. One cohort study in Germany found that *T. whipplei* was the fourth most frequently identified pathogen (6.3%) in bacterial endocarditis after streptococci, staphylococci and enterococci.¹² Other case series place the incidence between 2.6% and 7.1% in culture-negative cases.^{13 14} The gastrointestinal manifestations of the disease have

a preponderance for middle-aged men^{4 6} and this holds true for those affected by endocarditis in case series. Our patient is therefore unusual in that she is female. An interplay of environmental factors and immunogenetic susceptibility is thought to be responsible for developing the late-onset disease.

The clinical manifestations are varied, but valvular incompetence and heart failure are typical. In the case series by Fenollar *et al*⁵ of 28 patients, arthralgia was common (75%) and preceded the diagnosis by a mean 8 years. Fever was less frequent (25%–30%) and gastrointestinal symptoms were rare. Seventeen per cent of the Fenollar case series had embolic phenomena described, as in our patient's ulnar artery mycotic aneurysm. Interestingly, 19 of the 28 patients went on to have a small bowel biopsy which was universally negative for evidence of gastrointestinal Whipple's disease. Our patient has had no evidence of gastrointestinal involvement to date, although she has not had endoscopic studies. She describes an arthralgia affecting her shoulders of many years duration, and of uncertain aetiology, for which she had been given a diagnosis of osteoarthritis. This resolved after commencing antibiotics and this phenomenon has been described in previous case reports.¹⁴

Several studies have highlighted the difficulty in diagnosing endocarditis due to *T. whipplei* by the Duke criteria.^{5 15 16} The organism will not grow on standard culture, therefore three minor criteria are required in addition to evidence of endocardial involvement. As previously stated, fever is rare and microbiological evidence requires a high index of suspicion to perform the relevant investigations. Our patient had one major and one minor criterion, meeting the criteria for 'possible endocarditis'.^{7 16}

The diagnosis of Whipple's endocarditis is, therefore, mainly confirmed by surgically obtained specimens of the involved cardiac valves. Histopathological features include fibrosis and an infiltrate of foamy macrophages with inclusions staining positive by periodic acid-Schiff stain.^{4 8} Molecular analysis of the valves using a specific Whipple's PCR is the best diagnostic option, and it should be noted that PCR assays of blood samples show a low sensitivity for the disease.^{16 17} The diagnosis prior to cardiac surgery is therefore extremely challenging. Screening by PCR on saliva or stool has high specificity but very low sensitivity due to asymptomatic carriage between 1% and 30% of the population in prevalence studies.⁸

Investigating BCNE

This case highlights several pitfalls in the management of culture-negative endocarditis. The patient had three sets of peripheral blood cultures taken greater than 6 hours apart prior to initiation of antibiotics. In accordance with BSAC Guidance 2012,¹¹ these were not given extended incubation. Further blood cultures were not taken as the patient was afebrile and her inflammatory markers improved. There is variation among guidelines as to what further investigations should be performed in this circumstance. The European Society for Cardiology Guidelines (2015)¹⁸ suggest systematic serological testing for *Coxiella burnetii*, *Bartonella* spp., *Aspergillus* spp., *Mycoplasma pneumonia*, *Brucella* spp. and *Legionella pneumophila*, followed by specific PCR assays for *T. whipplei*, *Bartonella* spp. and fungi (*Candida* spp., *Aspergillus* spp.) from the blood according to local epidemiology. The BSAC guidelines (2012)¹¹ recommend serological testing for *Coxiella* and *Bartonella* in cases of BCNE, and then only if these are negative proceeding to testing for *Chlamydia*, *Legionella*, *T. whipplei* and *Mycoplasma*, due to the extreme

rarity of endocarditis caused by these organisms and the risk of false-positive serology leading to erroneous therapy. Our patient had blood testing by PCR for *T. whipplei* after the diagnosis was reached (and after 6 weeks of antibiotic therapy) which was negative, and we are unable to argue that earlier diagnosis would have been possible had these guidelines been followed.

The BSAC guidelines do recommend investigation of excised heart valve tissue by both culture and histological examination. Histological examination of our patient's valve may have demonstrated characteristics of Whipple's as described above, but was not requested. Culture of valvular tissue was performed and was negative, although guidelines comment on the relatively poor predictive value due to both prior antibiotic surgery causing false-negative results, and contamination during surgical manipulation leading to false positives.^{11 18}

Broad-range PCR, where DNA is extracted from homogenised tissue and subjected to PCR using broad-range primers targeting the bacterial DNA that codes for the 16S ribosomal subunit (16S rDNA), is of proven diagnostic value and is now included as a minor diagnostic criterion in the modified Duke criteria.¹⁹ Molecular methods are particularly useful after prior antimicrobial therapy, as detectable microbial DNA has been shown to persist long term in vivo even after successful therapy and is also beneficial for identifying pathogens that are not readily cultured with current methods.^{8 17 20} PCR is not without drawbacks. These include the need for appropriate expertise, false positives and PCR contamination as the *T. whipplei* bacterium can be present in water.⁵

PCR testing on heart valves is not done routinely at our laboratory and requires clinical suspicion of endocarditis with negative cultures. Currently, PCR testing on cardiac valves is only performed on a case by case basis following discussion with the microbiologist. Often it is too late to perform 16S PCR as samples have been put into enrichment broth. The UK Standards for Microbiology Investigations²¹ highlights the importance of storing heart valves for up to 1 month in the event 16S PCR testing is required, particularly as resampling is not an option in such situations. This case emphasises the need to update local laboratory protocols in line with national guidelines in order to make complex diagnoses such as Whipple's endocarditis and ultimately improve patient outcome.

Treatment of Whipple's endocarditis

Currently there is no standardised treatment of Whipple's endocarditis. *T. whipplei* is susceptible in vitro to doxycycline, sulfamethoxazole, penicillin, third-generation cephalosporins, carbapenems, aminoglycosides and chloramphenicol.^{2 17} This may explain the improvement seen clinically and biochemically in our patient following initial treatment with amoxicillin and gentamicin. Some authors recommend 2 weeks of intravenous ceftriaxone followed by oral trimethoprim-sulfamethoxazole for 12 months.^{8 22} Others have proposed 18–24 months of treatment and a consideration for lifelong suppression.¹⁴ Alternative treatment regimens proposed include intravenous meropenem followed by a combination of oral doxycycline and hydroxychloroquine as oral therapy.^{4 22} As our patient was very well clinically, and had received 6 weeks of intravenous therapy with amoxicillin and gentamicin preoperatively, we opted to treat her with oral trimethoprim-sulfamethoxazole with a planned duration of 1 year. At that point, the plan would be to have an open discussion with the patient regarding risks and benefits of continuing therapy to allow her to make an informed choice.

Patient's perspective

In the beginning, we attributed the pain to ongoing arthritis problems, but it very soon became obvious that there was something more serious going on. From being diagnosed with the aneurysm, it was a very frightening experience, as I hadn't experienced anything like it before. The operation to remove the aneurysm and the 6 weeks in hospital being given intravenous antibiotics every 4 hours to clear the infection was particularly hard. Awaiting the replacement of the heart valve was quite unnerving as we did not fully understand the procedures involved and whether any illness which developed prior to the operation could be detrimental to health. On receipt of the new valve, I was worried about needing to go on to warfarin but was assured that it was essential to prevent blood clotting on the new valve, even with a risk of bleeding. It was a very emotional experience for both my husband and I, not knowing exactly what the outcome would be from the infection and valve replacement, but having to face it anyway. Other than the clicking of the valve (especially audible at night) being weird but somehow comforting, we feel very lucky to have survived these traumatic events.

Learning points

- Consider Whipple's disease in culture-negative cases of endocarditis. A history of unexplained arthralgia may be a useful diagnostic clue.
- When considering the possibility of a mycotic aneurysm from an embolic source, the importance of sending tissue for microbiological and histological examination cannot be overstated.
- All cases of culture-negative endocarditis should have explanted valvular material examined both histologically and by microbiology using both standard and molecular methods where available.
- Gastrointestinal involvement seems more likely to be absent than present in cases of endocarditis due to *Tropheryma whippelii*.

Contributors IH coordinated the patients microbiological investigations, was involved in managing the patient postoperatively and obtained the patients consent for publication. OS managed the patient postoperatively and helped the patient provide her perspective. OS and IH jointly prepared the manuscript for publication.

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REFERENCES

- 1 Renon VP, Appel-Da-Silva MC, D'Incao RB, *et al*. Whipple's disease: rare disorder and late diagnosis rev. *Ins.tMed.Trop. SaoPaulo* 2012;54:293–7.
- 2 Whipple G. A hitherto undescribed disease characterised anatomically by deposits of fat and fatty acids in the intestinal and mesenteric lymphatic tissues. *John Hopkins Hosp Bull* 1907;109:382–93.
- 3 Relman DA, Schmidt TM, MacDermott RP, *et al*. Identification of the uncultured bacillus of Whipple's disease. *N Engl J Med* 1992;327:293–301.
- 4 Mandell GL, Bennett JE, Dolin R. *Principles and practice of Infectious Diseases*. 7th edition. Philadelphia: Churchill Livingstone, Elsevier, 2010 1:1435–41.
- 5 Fenollar F, Lepidi H, Raoult D. Whipple's endocarditis: review of the literature and comparisons with Q fever, bartonella infection, and blood culture-positive endocarditis. *Clin Infect Dis* 2001;33:1309–16.
- 6 Love SM, Morrison L, Appleby C, *et al*. Tropheryma whippelii endocarditis without gastrointestinal involvement. *Interact Cardiovasc Thorac Surg* 2012;15:161–3.
- 7 Durack DT, Lukes AS, Bright DK. New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. Duke Endocarditis Service. *Am J Med* 1994;96:200–9.
- 8 Fenollar F, Puechal X, Raoult D, *et al*. Whipple's disease. *N Engl J Med* 2007;56:55–66.
- 9 Fenollar F, Célard M, Lagier JC, *et al*. Tropheryma whippelii endocarditis. *Emerg Infect Dis* 2013;19:385–9.
- 10 Berent R, Auer J, Lassnig E, *et al*. Whipple's disease: misdiagnosed as sarcoidosis with further tricuspid valve endocarditis and pulmonary embolism - a case report. *BMJ Case Rep* 2009;2009 Epub ahead of print 1 Jun 2009.
- 11 Gould FK, Denning DW, Elliott TS, *et al*. Guidelines for the diagnosis and antibiotic treatment of endocarditis in adults: a report of the working party of the british society for antimicrobial chemotherapy. *J Antimicrob Chemother* 2012;67:269–89.
- 12 Geissdörfer W, Moos V, Moter A, *et al*. High frequency of *Tropheryma whippelii* in culture-negative endocarditis. *J Clin Microbiol* 2012;50:216–22.
- 13 Fournier PE, Thuny F, Richet H, *et al*. Comprehensive diagnostic strategy for blood culture-negative endocarditis: a prospective study of 819 new cases. *Clin Infect Dis* 2010;51:131–40.
- 14 Gruber JR, Sarro R, Delaloye J, *et al*. Tropheryma whippelii bivalvular endocarditis and polyarthralgia: a case report. *J Med Case Rep* 2015;9:259.
- 15 Feurle GE, Junga NS, Marth T. Efficacy of ceftriaxone or meropenem as initial therapies in Whipple's disease. *Gastroenterology* 2010;128:478–86.
- 16 Millar B, Moore J, Mallon P, *et al*. Molecular diagnosis of infective endocarditis-a new Duke's criterion. *Scand J Infect Dis* 2001;33:673–80.
- 17 Chan V, Wang B, Veinot JP, *et al*. Tropheryma whippelii aortic valve endocarditis without systemic Whipple's disease. *Int J Infect Dis* 2011;15:e804–e806.
- 18 Habib G, Lancellotti P, Antunes MJ, *et al*. 2015 ESC guidelines for the management of infective endocarditis. *Eur Heart J* 2015;36:3075–128.
- 19 Js L, Sexton DJ, Mick N, *et al*. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *CID* 2000;30:633–8.
- 20 Grijalva M, Horváth R, Dendis M, *et al*. Molecular diagnosis of culture negative infective endocarditis: clinical validation in a group of surgically treated patients. *Heart* 2003;89:263–8.
- 21 Public Health England. Standards for microbiology investigations online. 2014 <https://www.gov.uk/government/collections/standards-for-microbiology-investigations-smi> (accessed 4 Jan 2017).
- 22 Weisman A, Rebeck G, Morris A, *et al*. Whipple's endocarditis: an enigmatic cause of culture-negative bacterial endocarditis. *Can J Infect Dis Med Microbiol* 2013;24:29–e30.

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