Atypical presentation of *Abiotrophia defectiva* infective endocarditis in an octogenarian

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Abstract

Abiotrophia defectiva (A defectiva), a rare cause of bacterial infective endocarditis(IE) often presents with pyrexia and florid sepsis. This case highlights that *A defectiva* IE can present non-specifically in older frail patients without classical clinical findings. *A. defectiva* may be associated with a high proportion of culture-negative IE.

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Keywords: infective endocarditis, *Abiotrophia defectiva* , nutritionally-variant Streptococci, older patients, atypical presentation

Key Clinical Message

Blood cultures should be performed in non-specifically unwell older adults following non**-s** pecific presentations.

Prompt diagnosis and commencement of targeted antimicrobial therapy is essential in older patients with *A. defectiva* IE.

Introduction:

A. defectiva, is an organism which is part of the normal flora of the intestinal tract, oral cavity and urogenital tract [1]. It accounts for up to 6% of streptococcal infective endocarditis (IE) and has also been proposed as a possible pathogen in culture-negative endocarditis [2].

Classified as a nutritionally variant streptococcus (NVS),*A.defectiva* can have devastating implications if missed due to its high frequency of septic embolisation [3]. A case of aortic valve infective endocarditis in an 87-year-old lady with a background history of severe aortic stenosis (AS) who presented atypically with

bleeding per rectum (PR) and functional decline is described. The patient gave written informed consent to reporting her clinical and laboratory data as well as her radiographic images.

Case History:

An 87-year-old lady self-presented to the emergency department (ED) with a three-day history of bleeding PR associated with general malaise, subacute weight loss of 5 kg over three months and functional decline over a five-week period.

This octogenarian was frail (Clinical Frailty Scale score: 8) pre-admission with known severe aortic stenosis. Past medical history was otherwise significant for IHD with percutaneous coronary intervention five months previously, diverticular disease, anal squamous cell carcinoma (treated definitively with radiotherapy), dystonic tremor, hypertension and an 80 pack-year smoking history.

The patient denied any significant abdominal pain and had stable exertional dyspnoea without any recent deterioration in symptoms. Initial physical examination revealed a blood pressure of 116/50mmHg and heart rate of 82 beats per minute, an ejection systolic and early diastolic murmur consistent with mixed aortic valve disease and none of the stigmata of IE such as splinter haemhorrages, janeway lesions etc. There was no recorded pyrexia with a temperature of 36.7degrees C and the patient denied any recent history of rigors. There was pallor and mild generalised abdominal tenderness on palpation. In the ED, she had blood cultures as part of her unwell adult (without obvious clinical cause) investigations, part of the protocol within our service. Intravenous (IV) co-amoxiclav 1.2g three times daily was commenced for suspected acute diverticulitis. This lady was anaemic on admission, with a haemoglobin of 7.7g/dL (reference range 12 - 15 g/dl), necessitating transfusion of one unit of red cell concentrate (RCC).

Both anaerobic and aerobic bottles of admission blood cultures flagged positive at 14 hours with Gram-positive cocci in pairs and chains, which later cultured on chocolate agar and identified as *A. defectiva*(Figure 1) Other laboratory values on admission included: white blood cell count (WBC) of 11.6 x 10^9/L (reference range 4 - 10 x 10^9/L), absolute neutrophil count of 9.24 x 10^9/L (reference range 2 - 7 x 10^9/L), mean corpuscular volume 85.0 fl (reference range 84 - 96 fl), platelet count of 320 x 10^9/L (reference range 150 - 400 x 10^9/L), serum C-reactive protein of 62 mg/L (reference range 0 – 5 mg/L), blood urea nitrogen of 8.6 mmol/L (reference range 2.9 – 8.2 mmol/L), serum creatinine of 108 μmol/L (reference range 49 – 90 μmol/L), serum albumin 31 g/L (reference range 39 – 51 g/L), and serum ferritin 1015 ng/mL (reference range 10 - 200 μmol/L). The haematological and biochemical parameters of the patient are tabulated in Table 1.

Thereafter, the patient had two episodes of bleeding PR with associated fall in haemoglobin and RCC transfusion. She underwent an oesophagogastroduodenoscopy on day five of admission, which did not reveal any active/recent bleeding or ulceration.

The patient stabilised over the next 48 hours with clinical improvement but then had further bleeding PR, although remaining haemodynamically stable. She was unfit for bowel preparation and/or colonoscopy. Computed tomography (CT) scans of the abdomen and pelvis were performed to investigate ongoing gastrointestinal(GI) blood loss against a background of subacute weight loss. This revealed appearances consistent with multiple splenic infarcts (Figure 2) and diverticular disease. Concurrently with the identification of splenic infarcts, the patient had further bleeding PR with requirement for 2 further units of RCC transfusion and developed clinical sepsis, evidenced by fluctuating consciousness, mild hypoactive delirium, tachycardia and low-grade pyrexia.

The combination of *A. defectiva* bacteraemia with ongoing pyrexia, known aortic murmur and apparent splenic infarcts on CT scan prompted the decision to treat as infective endocarditis (IE), as advised by Clinical Microbiology. Ceftriaxone 2 grams once daily was started empirically while sensitivity tests were pending. Transthoracic echocardiogram revealed a large mobile echo-density suggestive of a vegetation on a stenotic (maximum gradient 74mmHg) aortic valve with evidence of aortic regurgitation (Figure 3A). A diagnosis of *A. defectiva* IE was made. The Infectious Disease team was consulted and intravenous

antimicrobial therapy was switched to amoxicillin 1 gram every four hours and gentamicin 50 milligrams three times daily, with monitoring of gentamicin serum levels as per protocol. A CT scan of the brain revealed no radiographic evidence of septic emboli in the brain parenchyma, a complication frequently associated with *A. defectiva* endocarditis [4].

The patient was deemed not to be a candidate for valve replacement given her frailty and significant pre-morbid co-morbidities. However, an initial clinical and biochemical response to antimicrobial therapy was noted.

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Unfortunately, on day 15, the patient had further bleeding PR with a drop in Hb necessitating further RCC transfusion. Later that day, she was found pulseless and unresponsive and, being declared Not for Active Resuscitation, she died peacefully on the ward. She had a post-mortem which confirmed severe aortic stenosis with calcification and vegetation of the valve leaflets grossly and microscopically (Figure 3B-D) and severe widespread critical coronary atherosclerosis adjacent to coronary stents associated with 90% occlusion involving the three coronary vessels (Figure 4). There was no evidence of acute ischaemic changes within the heart. The entire aorta showed severe calcified atheroma. There was no bleeding focus found in the upper gastrointestinal(GI) tract, small bowel or large bowel which demonstrated mild diverticular disease. No evidence of recurrent tumour within the anal area which revealed evidence of internal haemorrhoids (Figure 5).

Unexpectedly, the spleen showed no evidence of infarction on detailed examination grossly and microscopically. Kidneys showed granular cortical surfaces with evidence of hypertensive changes represented by thickened blood vessels. Lethal cardiac arrhythmia secondary to severe triple coronary atheroma was the most likely cause of death.

Discussion:

This frail octogenarian presented non-specifically, with relatively limited haematological and biochemical derangement of acute phase reactants associated with symptoms of bleeding PR, functional decline and anaemia. The initial working diagnosis was acute diverticulitis with associated sepsis. While the patient had initial clinical improvement on IV co-amoxiclav, she had further bleeding PR and evidence of sepsis following a switch to oral antibiotics prompting further imaging of the abdomen and subsequently the heart. The confirmation of *A. defectiva* bacteraemia with known AS and evidence of potential embolisation prompted the investigations which lead to a diagnosis of aortic valve IE. Following the initiation of penicillin-based antimicrobial therapy repeat blood cultures were sterile. Post-mortem examination confirmed evidence of aortic valve IE with the likely cause of intermittent major PR bleeding being haemorrhoids. It is possible that the source of bacteraemia was secondary to bowel translocation in the context of recurrent haemorrhagic episodes.

A. defectiva is an NVS considered part of the normal flora of the oral cavity, GI and urogenital tract in humans. In 1961, Fenkel and Hirsch first isolated a series of satellite streptococci growing adjacent to larger bacteria on agar media. The larger colonies were noted to be supplementing the growth of the satellite bacteria, later termed NVS [1]. NVS was further speciated in 1991 by Bouvet et al. to *Streptococcus defectivus* and *Streptococcus adjacens*[5]. In 1995 a new genus of NVS was identified through 16S rRNA sequencing, named *Abiotrophia* [6]. Further sequencing carried out by Collins et al. brought about the reclassification of a number of*Abiotrophia* strains in 2000 and the *Granulicatella* genus was named [7].

Fastidious in nature, NVS characteristically require the addition of L-cysteine or pyridoxal to grow on blood agar [1,7]. Due to the variation in Gram stains, colony morphology and difficulty culturing by routine laboratory methods, NVS must be considered a potential pathogen in all culture negative endocarditis [1]. However, the introduction of molecular methods of identification such as matrix assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry has made it increasingly possible to identify these pathogens in the clinical laboratory by providing a rapid, accurate and cost effective means of bacterial

identification [9–11]. Following ionization of samples, isolates are separated according to mass and analysed by their 'time of flight' to the detector where sample analysis is cross referenced to a data base and the bacteria is matched and identified [8].

NVS account for 5-6% of all streptococcal endocarditis [1].*A. defectiva* is rarely cultured successfully and has been attributed to <1% of all bacterial endocarditis [9]. The organism has a number of virulence factors such as the production of exopolysaccharide and the ability to bind with fibronectin which may account for its propensity to adhere to heart valves and produce the associated embolic phenomenon which have been previously described [13,15,16]

Evidence suggests that resistance of *A. defectiva* to penicillin is increasing [10]. Alberti et al. carried out an extensive investigation of susceptibility patterns of a number of NVS. One third of the isolates examined in the study were susceptible to penicillin, 14% were resistant and the remaining 53% were of intermediate sensitivity. In general *A. defectiva* was found to be more resistant than *G. adiacens* with 18.9% of *A. defectiva*resistant to penicillin. No resistance of *A. defectiva* to third generation cephalosporins was observed whereas 50% of *G. adiacens* isolates were resistant to cefotaxime. All isolates were fully susceptible to meropenem and vancomycin [11]. Choice of antimicrobial treatment in the setting of NVS IE is often not straightforward, as guidelines on treatment vary and results of susceptibility testing can often be delayed if isolates are sent to reference laboratories for work-up. The European Society of Cardiology (ESC) recommend a number of antimicrobial treatment options including benzylpenicillin, ceftriaxone and vancomycin combined with an aminoglycoside for the first 2 weeks of treatment [12]. However the British Society of Antimicrobial Chemotherapy do not advise the use of ceftriaxone with gentamicin in the setting of prosthetic valve endocarditis or if there is an extra-cardiac focus of infection or if the person is deemed a candidate for surgery. This is due the risk of nephrotoxicity and *Clostridium difficile* infection [12]. The isolate in this case report was sensitive to both penicillin and ceftriaxone with minimum inhibitory concentrations of 0.125 mg/L and 0.5mg/L respectively. Despite the sensitivity of this organism the clinical outcome was poor, reflecting the frequent presence of life threatening comorbidities in older patients, such as severe IHD in this case as well as the high pathogenicity and virulence of NVS which is independent to its antimicrobial sensitivity.

There are over one hundred-case reports of *A defectiva*deep-seated infection in the literature. These range from quadruple-valve endocarditis, vertebral osteomyelitis to endophthalmitis and peritonitis [15, 21–23]. This pathogen affects all age groups from young children to very old patients [13]. However outcomes in children are much better as surgical intervention is generally successful despite the presence of embolic complications [14]. The sudden mortality of this case is consistent with other case reports of this age-group and is often a reflection of the high rates of valvular endothelial damage observed in patients over the age of 60, or severe comorbidities as in this case [19,26].

The vast majority of NVS endocarditis cases evaluated in the literature refer to presentations with pyrexia associated with features of septic shock and heart failure [15]. Cases of *A. defectiva* IE reported often involve immunocompromised patients and/or the presence of non-native or structurally defective valves. ?need reference

The atypical presentation of this older patient with non-specific symptoms represents an unusual manifestation of infection with a rare organism which classically presents with more florid signs of sepsis often with devastating consequences. Given the difficulty with culture and identification of this organism, it is likely that *A. defectiva* may be associated with a higher proportion of culture-negative IE than previously reported [16]. Moreover, it is conceivable that the prevalence of *A. defectiva* infection in older patients is higher than reported in the literature.

In this case an intra-abdominal source of sepsis was thought to be likely. Persistent bleeding PR during the patient's admission against a background of apparent septic splenic emboli, raised the possibility of colonic septic embolisation with associated bowel ischaemia. However, the patient's serum lactate level was always within normal parameters and her clinical status was not consistent with extensive bowel ischaemia. Unfor-

tunately, she was unfit for proctoscopy, sigmoidoscopy or colonoscopy but acute diverticulitis and/or colonic carcinoma were the most plausible clinical causes for bleeding PR. However, at post-mortem, haemorrhoids were the likely actual source, with no pathological evidence of bowel ischaemia, tumour or diverticulitis. This suggests that bacterial translocation from the lower GI tract was the most likely source of bacteraemia.

This pathogen is rarely identified clinically and can have devastating complications often associated with septic embolisation in up to one third of cases [17]. This case highlights the importance of performing blood cultures in non-specifically unwell older adults and cardiac imaging, especially with known or suspected valvular disease. The patient, albeit frail and unfit for invasive tests, responded to IV antibiotics and was returning towards her baseline functional status, emphasising the importance of accurate diagnosis and definitive treatment in this frequently encountered population. Her pre-existing established severe IHD was the likely attributable cause of death, probably resulting in fatal arrythmia.

Prompt diagnosis, pathogen isolation and commencement of targeted antimicrobial therapy is essential in older patients with *A. defectiva* IE. This is particularly important in order to prevent potentially fatal complications, since presenting symptoms are highly variable and, non-specific especially in older patients.

Author Contribution:

Gerard Forde: Conceptualization (lead); writing – original draft (lead); writing – review and editing (equal)

Mary Lucey: Conceptualization (secondary); writing – original draft (secondary)

Paula M O Shea: Data curation (lead); formal analysis (lead)

Ramadan Shatwan: Writing – original draft (secondary); resources (lead)

Julie Okiro: Conceptualization (secondary); writing – review and editing (equal)

Eamon C Mulkerrin: Supervision (lead); concetualization (secondary); writing – review and editing (equal)

Conflict of Interest Statement:

The authors have no conflicts of interest to disclose.

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Table 1: Routine haematological and biochemical investigations from admission to day 15 of hospitalisation

Laboratory parameter (Unitage)	**Reference Interval**	**Day 1**	**Day 2**	**Day 5**	**Day 7**	**Day 8**	**Day 10**	**Day 15**
		Admission Low Hb: 1 unit of RCC	*IV Coamoxi-clav 1.2g tds for 5d	OGD No active/ recent bleeding/ ulceration	CTAP Revealed multiple splenic infarcts & diverticula disease During the afternoon the patient suffered an additional bleeding PR: 1unit of RCC given overnight	1 unit of RCC	@08:00h Oral Coamoxi-clav switched to IV Ceftriaxone 2g/d @ 14:00h TTE Revealed a large echo density suggestive for vegetation @ 16:30h *Amoxi-cillin 1g every 4h & Gentamicin 50mg tds	Further bleeding PR 1un RCC Pulse-le unrespo sive, declared dead (F in Peac
White Cell Count (10^9/L)	4 - 10	**11.6**	9.8	8.6	**10.6**	**9.9**	9.2	8.9
Neutrophil Count (10^9/L)	2 - 7	**9.2**	**7.6**	6.9	**8.8**	**8.2**	**7.6**	6.9
Haemoglobin (g/dL)	12 - 15	**7.7**	**8.5**	**9.7**	**9.0**	**8.2**	**8.6**	**9.2**
Mean corpus-cular volume (fL)	84 - 96	85	84	86	85	84	84	83
Platelet count (10^9/L)	150 - 400	320	263	327	338	312	292	231
C-reactive protein (mg/L)	<5	**62**	n/r	**52**	**37.8**	**33.3**	**25.7**	**19.6**
Serum Urea (mmol/L)	2.9-8.2	**8.6**	n/r	4.3	5.2	4.1	3.8	2.7

Laboratory parameter (Unitage)	**Reference Interval**	**Day 1**	**Day 2**	**Day 5**	**Day 7**	**Day 8**	**Day 10**	**Day 15**
Serum Creatinine (µmol/L)	49 - 90	**108**	n/r	60	59	61	58	58
Serum Albumin (g/L)	39 - 51	**31**	n/r	**32**	**32**	**30**	**27**	**23**
Serum Ferritin (ng/mL)	10 - 200	**1015**	n/r	n/r	n/r	n/r	n/r	n/r
Plasma Lactate (mmol/L)	0.6-1.4	n/r	n/r	nr	nr	0.8	0.8	n/r

*Hb: Haemoglobin, RCC: red cell concentrate, *: Commencement of antibiotic treatment, IV: intravenous, tds: three times daily, d: day, h: hour, OGD: Oesophago-Gastro-Duodenoscopy, CTAP: Computed tomography of the abdomen and pelvis, TTE: transthoracic echocardiogram*

n/r: not requested, Data in bold = abnormal values

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