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Title: Diabetic foot ulcer with Alcaligenes faecalis infection

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Abstract:

Background: Diabetic foot ulcers are an increasingly common complex problem and are associated with a very considerable health care burden. Diabetic foot ulcer with Alcaligenes faecalis infection is rarely reported in the literature. We report a case series of diabetic foot ulcer with Alcaligenes faecalis infection treated at our facility.

Methods: We conducted a retrospective analysis of all patients with diabetic foot ulcer with Alcaligenes faecalis infection seen from January 2014 to April 2019. We analyzed the clinical characteristics, ulcer lesion classification, comorbidities, prior intravenous antibiotic use within three months, wound culture, antibiotics sensitivity test, and clinical outcomes of these patients.

Results: Eight cases of diabetic foot ulcer with Alcaligenes faecalis infection were seen in five males and three females. The mean age was 54.6 years. All patients had other comorbidities, and all ulcer lesions were of chronic duration (more than 14 days). All wound cultures revealed polymicrobial infection, with two cases of diabetic foot with extensive-drug resistant Alcaligenes faecalis infection found in 2019. All patients needed intravenous antibiotic therapy and surgical interventions for the chronic ulcer lesion. The wound failed to heal in three patients.

Conclusions: All diabetic foot ulcers with Alcaligenes faecalis infection were of chronic duration (more than 14 days) and had polymicrobial infection.

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Extensive-drug resistant Alcaligenes faecalis emerged in 2019. Definitive antibiotic therapy is necessary for all infected wounds and should be based on both the culture results and susceptibility data. All patients will need appropriate wound care, and most will need rapid surgical intervention for an optimal outcome.

Key words:

1. Alcaligenes faecalis
2. Diabetic foot ulcer
3. Extensive-drug resistant,

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Abbreviations: DM=diabetes mellitus CMZ=cefmetazole, CEF=cefazolin, SAM=ampicillin-sulbactam ,OXA=oxacillin, CMZ=cefmetazole, CRO=ceftriaxone, CAZ=ceftazidime, GM=gentamicin, AN=amikacin, PIP=piperacillin, CIP=ciprofloxacin, LVX=levofloxacin, IMP=imipenem, MPM=meropenem, FEP=cefepime, TZP=piperacillin-tazobactam, VAN=vencomycin, TE=teicoplanin, Col=colistin TGC=tigecycline, DOR=Doripenem, MDR=multidrug-resistant, XDR= extensive-drug resistant, PDR=pandrug-resistant ESBL=extended-spectrum β-lactamase, S=sensitive, R=resistant, I=intermediate, HTN=hypertension, ESRD=end- stage renal disease, CKD=chronic kidney disease, CVA=cerebral vascular accident, PAD=peripheral arterial disease, CAD=coronary artery disease, VRE=vancomycin resistant enterococcus, MRSA=methicillin resistant staphylococcus aureus, GNB= Gram-negative bacillus. NA= not accessed.

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Text:

Introduction

Diabetic foot ulcers are an increasingly common complex problem and are associated with a very considerable health care burden.[1] Foot ulcer is the most frequent diabetes-related cause of hospitalization. The global prevalence of diabetic foot ulcer is 6.3%.[2] People with diabetes have about a 25% chance of developing a foot ulcer in their lifetime.[3] About half of diabetic foot ulcers are infected at presentation.[4] Acute infections in patients who have not recently received antimicrobials are often monomicrobial. Gram-positive cocci are the predominant organisms and Staphylococcus aureus is the most commonly isolated pathogen. Chronic infections are often polymicrobial, including Enterococci, Enterobacteriaceae, Pseudomonas aeruginosa, other non-fermenting Gram-negative bacilli, and obligate anaerobes.[5-9] Alcaligenes faecalis is a Gram-negative, obligate aerobe, oxidase-positive, catalase-positive, and non-fermenting bacterium commonly found in soil, water, and hospital environments. The organism has been isolated from a range of clinical materials such as urine, blood, wound discharge, stool, cerebrospinal fluid, and respiratory secretions.[10-12] A. faecalis has been associated with endocarditis, bacteremia, meningitis, endophthalmitis, skin and soft tissue infection, urinary tract infection, otitis media, peritonitis, and pneumonia.[13-20] We here report a series of

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patients with diabetic foot ulcer with A. faecalis infection, in order to improve the clinical care of such patients.

Methods:

We conducted a retrospective analysis of all patients presenting with diabetic foot ulcer with A. faecalis infection who were admitted to Dalin Tzu Chi Hospital from January 2014 through April 2019. Patients were diagnosed with diabetic foot ulcer with infection when their clinical symptoms and signs indicated skin and soft tissue infection, such as redness, warmth, induration, tenderness, ulcer lesion, abscess, gangrene, fasciitis, or osteomyelitis. Ulcer lesion classification was done by using the University of Texas wound classification system[21], and the Infectious Disease Society of America infected diabetic foot ulcer classification system[22]. The medical records of all patients were reviewed for demographic information, clinical symptoms and signs, comorbidities, use of intravenous antibiotics within three months, wound culture, antibiotics sensitivity test, and clinical outcomes. Superficial wound swab specimens were collected for culture. Specimens were obtained only after the wound was cleaned by povidone iodine solution and sterile saline. Wound swab specimens for antibiotic susceptibility were done using the Vitek II system with ASTGN87 cards (BioMérieux, Marcy-l'Étoile, France) with Clinical and Laboratory Standards Institute interpretive criteria M100-25th. Wound swab specimens were cultured as soon as they

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were collected, on chocolate agar, blood agar, Eosin Methylene Blue Agar, colistin-nalidixic acid agar plates, and thioglycollate broth. Gram staining and microscopy were prepared and read. The five culture mediums were incubated in a carbon dioxide-enriched atmosphere for 16-18 hrs. Then, a sterile swab stick was used to transfer a sufficient number of colonies of pure culture and to suspend the microorganisms in 3.0 mL of sterile saline (aqueous 0.45% to 0.50% NaCl, pH 4.5 to 7.0) in a 12 x 75 mm clear plastic test tube. The turbidity was adjusted to 0.50-0.63 McFarland Equivalence Turbidity Standard. Identification cards were inoculated with microorganism suspensions using an integrated vacuum apparatus. A test tube containing the microorganism suspension was placed into a cassette. One GN identification card (automated identification of 135 taxa of the most significant fermenting and nonfermenting Gram-negative bacilli) and another VITEK II AST-N322 card (for susceptibility testing of aerobic Gram-negative bacilli against specified antimicrobials) were placed in the neighboring slots, along with the transfer tube and the corresponding suspension tube. Calculations were performed on raw data and compared to thresholds to determine the reactions for each test.

Results:

Nine cases of A. faecalis skin and soft tissue infection were seen during the study period; A case was surgical wound infection. Eight cases were diabetic foot ulcer

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infection, including five male and three female patients. The mean age was 54.6 years (range: 41-85 years). All patients had other comorbidities. All patients' foot ulcer lesions were of chronic duration (more than 14 days) (range: 14 days to 18 months). Two patients had no history of prior intravenous (IV) antibiotics used within three months for their chronic ulcer lesion. All patient wound cultures displayed polymicrobial infection. The antibiotics sensitivity test showed the presence of extensive drug-resistant (XDR) A. faecalis beginning in 2019. Two patients did not receive adequate antibiotic therapy. Case 4 was treated with oxacillin and cefmetazon, which do not treat A. faecalis. Case 7 was treated with ceftazidime and vancomycin, which do not treat A. faecalis and Acinetobacter baumannii. All patients needed surgical intervention for their chronic ulcer lesions. The wound did not heal in three patients. Table 1 and Table 2 shows the clinical characteristics, treatment outcomes, and bacteriology of the eight patients with diabetic foot ulcer with A. faecalis infection.

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Table 1: Clinical characteristics and treatment outcome in eight cases of diabetic foot ulcer with *Alcaligenes faecalis* infection

	Case 1	Case2	Case 3	Case 4	Case 5	Case 6	Case7	Case8
year	2014	2015	2015	2017	2018	2018	2019	2019
Duration of wound	14 days	5 mos	1 mo	3 mos	14 days	12 mos	14 days	18 mos
comorbidities	DM HTN	DM HTN ESRD CVA	DM CKD CVA	DM HTN	DM PAD ESRD CAD	DM CKD	DM HTN ESRD PAD	DM PAD CKD
Ulcer lesion	+	+	+	+	+	+	+	+
abscess	nil	+	nil	+	nil	+	+	nil
cellulitis	+	+	nil	nil	nil	nil	nil	+
Necrotizing fasciitis	nil	+	+	nil	+	nil	+	+
Osteomyelitis	nil	nil	+	+	nil	nil	nil	nil
gangrene	nil	+	nil	nil	+	nil	+	+
Texas wound classification system	2B	2D	3B	3B	2D	2B	2D	2D
IDSA classification of infected DFU	MOD Class B	MOD Class B	MOD Class B	MOD Class B	Severe C	MOD Class B	MOD Class B	MOD Class B
Treatment	SAM	MPM VAN	VAN CAZ	OXA CMZ	MPM VAN	CAZ TEC	CAZ VAN	COL
Operation	DEB	DEB	SQE	DEB	AMP	DEB	DEB	DEB
outcome	heal	heal	heal	heal	no heal	no heal	heal	no heal

DEB: debridement

SQE: sequestrectomy

AMP: amputation

IDSA: Infectious Disease Society of America

DFU: diabetic foot ulcer

MOD: moderate

mo: month

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Table 2: Bacteriology in eight cases of diabetic foot ulcer with *Alcaligenes faecalis* infection

	Case 1	Case2	Case 3	Case 4	Case 5	Case 6	Case7	Case8
year	2014	2015	2015	2017	2018	2018	2019	2019
prior intravenous antibiotics used within three months	CIP SAM	PIP CRO VA	NIL	CEF TEC	NIL	CAZ, CIP PIP TEC	CAZ VAN	LVX MPM TEC
Results of antibiotics sensitivity test of *Alcaligenes faecalis*								
GM	S	S	S	R	S	I	R	R
AN	S	S	S	S	S	S	R	R
CAZ	S	S	S	S	S	S	R	R
FEP	S	S	S	I	S	I	R	R
SAM	S	S	S	I	S	S	R	R
TZP	S	S	S	I	S	S	R	R
CIP	S	S	S	R	S	R	R	R
IPM	S	S	S	S	S	S	R	R
MPM	S	S	S	S	S	S	R	R
TGC	NA	NA	NA	NA	NA	NA	NA	S
Mixed infection pathogens								
Enterococcus	V				V			V
Proteus vulgaris		V			V			
Citrobacter koseri			V					
MRSA			V					
Klebsiella pneumoniae						V	V	V
Providencia rettgeri						V		
Acinetobacter baumannii							V	V
Morganella morganii				V				
Staphylococcus epidermis				V				

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Discussion

The literature shows 12 cases of skin and soft tissue A. faecalis infection, including four cases of toe web infection, [23] one case of dog bite cellulitis,[24] two cases of surgical wound infection,[17] one case of superinfection in the foot tinea pedis,[17] and four cases of diabetic foot ulcer infection.[13,15,17] Other studies and our case series indicate that diabetic foot ulcer accounts for 57.1% of A. faecalis infections in skin and soft tissue. In 1997, Bizet reported a case of a 64-year-old male with insulin-dependent diabetes and left foot ulcer with A. faecalis infection. The patient was treated with IV amoxicillin-clavulanic acid for ten days.[13] In 2014, Tena reported two cases of diabetic foot ulcer with A. faecalis infection, all with polymicrobial infection. All strains of A. faecalis were susceptible to amoxicillin-clavulanic acid. One case was a cured foot ulcer, and the other case was a recurrence of foot ulcer.[17] In 2019, Chua reported a case of a 63-year-old female with a diabetic foot ulcer with extended spectrum beta-lactamase (ESBL)-producing A. faecalis infection. He suggested that imipenem and meropenem may be considered as agents of choice for an ESBL-producing A. faecalis infection.[15] In our series, all cases had an ulcer lesion of chronic duration (more than 14 days) and all had mixed infection with other bacteria. The most common additional pathogens were Enterococcus, Klebsiella pneumoniae, Proteus vulgaris, and A. baumannii. Gram-negative bacilli account for

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71.4% of mixed infection pathogens. In 2017, the first case with A. faecalis resistant to gentamicin and ciprofloxacin was reported. Unfortunately, the diabetic foot ulcer with XDR A. faecalis infection emerged in 2019 and IV tigecycline or colistin was needed to treat it. There is no literature on XDR A. faecalis diabetic foot ulcer infection, but two cases of XDR A. faecalis pneumonia and one case of pandrug-resistant A. faecalis bacteremia have been reported.[19,20,25] In 2010, Junejo reported on a 73-year-old male with A. faecalis pneumonia. The sensitivity analysis of sputum culture showed that the isolated A. faecalis was resistant to anti-pseudomonas penicillins, carbapenems, aminoglycosides, and quinolones. The patient was treated with polymyxin B and became hemodynamically stable.[19] In 2016, Agarwal reported on a 32-year-old man with Dengue hemorrhagic fever and pneumonia. Bronchoalveolar lavage fluid culture isolated A. faecalis, and the antibiotic sensitivity test showed sensitivity to colistin and tigecycline only. Colistin and meropenem were given, but the patient later succumbed to his illness.[20] In our Case 7 and Case 8, the antibiotic sensitivity test was the same as in the cases of Agarwal and Junejo. In 2019, Hasan reported a 60-year-old female with pandrug-resistant A. faecalis who was treated with double-dose tigecycline and had a successful treatment outcome.[25] It was terrible that pandrug-resistant Alcaligenes faecalis pathogen had been found. We emphasize that A. faecalis has emerged as a pathogen resistant to commonly used

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antibiotics such as anti-pseudomonas penicillins, carbapenems, aminoglycosides, and quinolones. It is too early to know the pathogenesis of emerging multidrug-resistant A. faecalis. The medical community urgently needs microbiologists to explore the pathogenesis of emerging multidrug-resistant A. faecalis, so as to control this pathogen.

Although Case 4 and Case 7 did not receive adequate IV antibiotics to treat the A. faecalis infection, they received surgical intervention and wound care. Their diabetic foot ulcer infection were healing. Their diabetic foot ulcer were local infection that could cure by adequate debridement and appropriate wound care.This result stresses that wound care and surgical interventions are important in treating diabetic foot ulcer infections. In three cases, the diabetic foot ulcer did not heal. Case 5 had wound infection complicated by septic shock. This patient had to undergo right lower leg below the knee amputation to save her life. Case 6 had the comorbidities of peripheral artery disease (PAD) and chronic kidney disease (CKD). The duration of his diabetic ulcer lesion was 12 months. The patient received IV antibiotics with ceftazidime and tigecycline therapy, as well as debridement, but the leg ulcer lesion still failed to heal. Case 8 had comorbidities of PAD, CKD, bed-ridden hypoxic encephalopathy, and prolonged mechanical ventilation. The duration of his diabetic ulcer lesion was 18 months. The ulcer lesion showed infection with XDR A. faecalis. The patient was

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treated with IV colistin and wound debridement, but the ulcer lesion still failed to heal. Two of the three cases that failed to heal had PAD comorbidity and the two cases did not undergo any revascularization procedures. PAD may be an influent factor of poor wound healing in diabetic foot ulcer. The study by Brevhow found that the severity of PAD significantly influences the ability of diabetic foot ulcer to heal.[26] Weck reported that poor wound healing is often aggravated by the comorbidity of PAD.[27]

The infection of diabetic foot ulcers may contribute to delayed healing. Optimal management of diabetic foot infections can reduce the incidence of infection-related morbidities and the incidence of limb amputation. Antibiotic therapy is necessary for all infected wounds. Definitive therapy should be based on both the culture results and susceptibility data. It is important to remember that all patients will need appropriate wound care and most will need rapid surgical intervention.

Limitations

Our case series report of diabetic foot ulcer with A. faecalis infection is small and therefore can provide only minimal clinical experience. Additional reports of diabetic foot ulcer with A. faecalis infection will add to the knowledge of how to treat this multi-resistant pathogen infection.

Conclusion

Diabetic foot ulcer with A. faecalis infection is rarely reported in the literature. XDR

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A. faecalis has emerged recently in our hospital. Diabetic foot ulcer with A. faecalis infection is common in those with an ulcer lesion of chronic duration (more than 14 days) and infections are commonly polymicrobial. Adequate antibiotic treatment, appropriate wound care, and surgical intervention are all crucial for healing.

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Declarations:

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Ethics approval and consent to participate:

The project was approved by Buddhist Dalin Tzu Chi general hospital research ethics committee. (Approved IRB No.: B10802024))

Availability of data and materials:

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions:

CH designed the study, collected the data, analyzed the data, wrote the manuscript, and reviewed the manuscript. All authors contributed to preparing the manuscript. All authors read and approved the final manuscript.

Consent for publication:

Not applicable.

Competing interests:

The authors declare that they have no competing interests

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