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Brief report

Bacteremic pneumonia caused by *Enterococcus hirae* in a subject receiving regorafenib

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ABSTRACT

Introduction: Infections due to *Enterococcus hirae* have rarely been reported in humans but are not uncommon in mammals and birds. We describe a case of *E. hirae* bacteremia and pneumonia in a bird breeder and its potential relationship with regorafenib, a tirosin kinase inhibitor (TKI).
Methods: Descriptive study and review of the literature through a PubMed search of the cases described previously to date.
Results: Only seventeen cases have been described, mainly endocarditis, pyelonephritis, and intraabdominal infections. No cases of pneumonia have been reported so far. The recent increase in TKI use opens a new field to explore in infectious diseases due to both the exposure to these immunosuppressive drugs and the increased survival of subjects with severe underlying comorbidities.
Conclusion: In patients in contact with birds, immunosuppressed by their underlying morbidities and treated with regorafenib, clinicians should be aware of an increased risk of unusual potentially severe infections.

Neumonía bacteriémica causada por *Enterococcus hirae* en un paciente tratado con regorafenib

Palabras clave:
Enterococcus hirae
Regorafenib
Inhibidor de la tirosina quinasa

RESUMEN

Introducción: La infección por *Enterococcus hirae* se ha reportado raramente en humanos, pero no es infrecuente en mamíferos y aves. Describimos un caso de neumonía bacteriémica por *Enterococcus hirae,* y su posible relación con regorafenib, un inhibidor de la tirosina quinasa (TKI, por sus siglas en inglés).
Métodos: Estudio descriptivo y revisión de la literatura mediante una búsqueda en PubMed de los casos descritos anteriormente hasta la fecha.
Resultados: Solo se han publicado 17 casos, principalmente endocarditis, pielonefritis e infecciones intraabdominales, sin ningún caso de neumonía. El reciente incremento en el uso de la TKI abre la puerta a un nuevo campo a explorar en enfermedades infecciosas debido tanto a la exposición a estos fármacos como al incremento en la supervivencia de individuos con importantes comorbilidades subyacentes.
Conclusión: En pacientes en contacto cercano con aves, inmunodeprimidos por sus comorbilidades y en tratamiento con regorafenib, podría existir un mayor riesgo de infecciones inusuales potencialmente graves.

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Introduction

Enterococci are Gram-positive facultative anaerobes and are part of the normal gut microbiota. The main species causing infections in humans are *Enterococcus faecalis* and *Eneterococccus faecium*.[1,2] In the last decade enterococci have been reported as the third most common cause of bacteraemia in humans.[3]

Enterococcus hirae is known to cause infections in psittacine birds but accounts for less than 1% of the enterococcal species isolated in human clinical samples.[4]

The first description of *E. hirae* infection in humans in 1998 reported a case of septicaemia in a patient with end stage renal disease in hemodialysis.[5] We report a case of bacteraemic pneumonia caused by *E. hirae* in a subject receiving regorafenib. We discuss the potential relationship between regorafenib exposure and the development of this rare cause of infection.

Case report

A 57-year-old man with a history of type 2 diabetes mellitus, chronic obstructive pulmonary disease (COPD), hepatic cirrhosis Child Pugh B secondary to hepatitis C virus (HCV) and chronic alcoholism. He developed a hepatocarcinoma stage BCLC C. Initially, he was treated with radiofrequency ablation and alcoholization of multinodular hepatocellular carcinoma. Subsequently, due to intractable multifocal tumor progression, the second line of treatment was sorafenib, which was suspended after a few months due to intrahepatic progression. Finally, regorafenib was started with a stable clinical response. At admission, he had received 8 months of regorafenib.

The last hospital admission was the month before, due to a bilateral bronchopneumonia caused by *Chlamydia psittaci*. Detection of *Legionella pneumophila* and *Streptococcus pneumoniae* antigens in urine was negative, as well as sputum bacilloscopy, and bronchoalveolar lavage screening for bacteria, mycobacteria and fungi. The patient was a goldfinch breeder and some of them were apparently ill, with active wing molt, and he had isolated them in a separate room.

The patient reported dyspnea, disorientation and fever during 2 days. He had a temperature of 38 °C, blood pressure 80/42 mmHg, heart rate 73 bpm, respiratory rate 32 min^{-1}; oxygen saturation at 95% on oxygen at 2 L/min. There were no abnormal cardiac murmurs and no clinical signs of infective endocarditis and bronchospasm. In the neurological examination he had grade 2 encephalopathy.

The laboratory data demonstrated: white blood cells 13 100/μL with left shift (neutrophils 82%), C-reactive protein of 31 mg/L, lactic acid 3.33 mmol/L, and bilirubin 3.65 mg/dL. The arterial gases demonstrated pO2 64 mmHg and pCO_2 36 mmHg with pH 7.46. Two sets of blood cultures obtained on admission yielded *Enterococcus* spp., which was identified at the species level as *E. hirae* by mass spectrometry (MALDI-TOF). The organism was susceptible to ampicillin, imipenem, gentamicin, ciprofloxacin, levofloxacin, vancomycin, teicoplanin, trimethoprim/sulfamethoxazole, linezolid and tigecyclin. Detection of *L. pneumophila* and *S. pneumoniae* antigens in urine was negative.

The chest X-ray showed a basal left condensation. Transthoracic echocardiogram study was normal, without vegetation images.

The patient was initially treated with intravenous piperacillin/tazobactam plus azithromycin and oral rifaximine. The treatment was subsequently de-escalated to amoxicillin-clavulanate for a total of 8 days. The infection was cured and control blood cultures were negative, with resolution of pneumonia.

Discussion

E. hirae, originally described in 1985, is known to cause infections in various animal species, but is infrequent in humans.[6] Only seventeen case reports of human infection due to this microorganism have been published to date (Table 1).[7] All cases reported to date describe bacteremia, associated with different clinical conditions including endocarditis, pyelonephritis, and intraabdominal infections, which in some cases progressed to septic shock. To our knowledge, no cases of pneumonia have been described so far. In our patient, the episode of pneumonia could not be explained by the previous episode of *C. psittaci* three weeks before, which resolved completely both clinically and radiologicaly. In addition, in the chest X-ray we observed a new basal left condensation not previously observed.

Although enterococci are not a usual cause of pneumonia, the findings on chest X ray with two positive blood cultures for *E. hirae*, as well as the negative results in all the microbiology work-up supported the diagnosis of *E. hirae* pneumonia.

In most cases reported, the source of *E. hirae* transmission to patients is unclear. Only one case reports an epidemiological contact with sick birds.[7] Therefore, the mechanism of transmission to humans remains largely elusive. The majority of patients had immunosuppression such as diabetes mellitus, alcoholic liver disease or chronic renal failure.

In our case, there was a clear epidemiological relationship, which was the contact with sick birds, the animals most frequently affected by this pathogen. *E. hirae* can produce encephalomalacia with vascular thrombosis and meningitis in birds.[8] The potential mechanism of transmission remains elusive, and both inhalation or direct skin contact could have a potential role. It is known that a prolonged hospital stay and a previous course of antibiotics can facilitate enterococcal infections. In this scenario, colonization by enterococci is a previous step for the development of the infection. We cannot rule out that our patient's skin was colonized by *E. hirae* from his sick birds.[9]

Enterococci are intrinsically resistant to different antibiotics such as cephalosporins and can acquire resistance to amoxicillin (through hiperproduction of PBP5) and aminoglycosides (through aminoglycoside-modifying enzymes). They also have a special ability to develop resistance to other antibiotics, either by acquisition of resistance genes located on plasmids or by spontaneous mutations. The ability of enterococci to survive in adverse conditions together with increasing numbers of patients with risk factors for an enterococcal infection (previous hospital admission, immunosuppression, previous use of antibiotics, etc.) has eventually increased the prevalence of infections due to these microorganisms. The acquired resistance to glycopeptides in enterococci can be attributed to the use of glycopeptide avoparcin in farms, the widespread use of vancomycin in clinical practice and the acquisition of resistance genes between different microorganisms.[10]

Agents targeting vascular endothelial growth factor (VEGF) – or specifically its tyrosine kinase domain (as well as those of other angiogenic signaling pathways) – have been developed in an attempt to improve antitumor efficacy and overcome resistance to VEGF blockade alone.[11]

Sorafenib, dasatinib, ruxolitinib, ibrutinib, tofazitinib, sunitinib, axitinib, and pazopanib are oral small-molecule tyrosine kinase inhibitors (TKIs) that have been associated with variable degrees of infectious complications, including fatal bacterial and fungal infections (particularly ibrutinib), with some contradictory results.[12] Some of them even have a black box warning in their package insert information endorsed by drug regulatory agencies.

VEGF TKI seem to modulate the functionality of T cells. It is unlikely however, that such an effect exerts a negative impact on host immunity. In fact, in vivo studies suggest that sorafenib

Table 1
Reported cases of human infections due to *Enterococcus hirae*. Updated from Paosinho et al.[7]

Reference	Year	Age (y)/sex	Diagnosis	Risk factor	Method of *E. hirae* identification	Clinical sample	Treatment
Gilad et al.[5]	1998	49/M	Septicemia	Hemodialysis catheter	Rapid ID 32 Strep system	Blood	Vancomycin
Park et al.[15]	2000	21/F	Acute pyelonephritis	None	(*sodA* gene) sequencing	Blood, urine	Ampicillin
Poyart et al.[16]	2002	72/M	Native valve Endocarditis	Coronary artery disease	(*sodA* gene) sequencing	Blood	Ampicillin, gentamicin, rifampin, vancomycin
Canalejo et al.[17]	2008	55/M	Spondylodiscitis	Diabetes mellitus	VITEK 2 automated system (bioMériux) rRNA gene sequencing	Blood	Ampicillin, gentamicin, levofloxacin, trimethoprim/sulfamethoxazole
Talarmin et al.[18]	2008	78/F	Prosthetic valve endocarditis	Diabetes mellitus, bioprosthetic valve	I6S rRNA sequencing	Blood	Ampicillin, gentamicin,rifampicin
Kim et al.[19]	2009	57/F	Acute pyelonephritis	Rheumatoid arthritis	Unknown	Blood, urine	Amoxicillin, ceftriaxone, ciprofloxacin
Benagli et al.[20]	2010	62/F	Acute pyelonephritis	None	BD Phoenix ID/AST Panel Inoculation System	Blood	Amoxicillin
Benagli et al.[20]	2010	86/F	Acute cholangitis	None	BD Phoenix ID/AST Panel Inoculation System	Blood	Cefmetazole
Sim et al.[21]	2012	61/M	Bacterial peritonitis	Liver cirrhosis	Automated MicroScan WalkAway system; suggar fermentation tests	Blood, ascitic fluid	Ampicilin
Brulé et al.[22]	2013	44/M	Bacteremia, Pyonephrosis	Alcoholic liver disease	Gel electrophoresis	Blood, urine, kidney biopsy	Amoxicillin, ceftriaxone, amikacin
Salem-Bekhit et al.[23]	2013	56/M	Native valve endocarditis	Diabetes, cardiac arrhythmia with surgical ablation	Unknown	Blood	Ampicillin, rifampin, amoxicillin
Bourafa et al.[24]	2013	50/M	Symptomatic lower UTI	BPH, diabetes mellitus, urinary catheterization	MALDI-TOF MS	Urine	Ampicillin, gentamicin
Alfouzan et al.[25]	2014	48/F	Multiple splenic abscesses	Diabetes mellitus type 2	BD Phoenix Automated Microbiology System, and DNA sequencing	Blood	Vancomycin, ampicillin
Paosinho et al.[7]	2016	78/F	Acute pyelonephritis	Atrial fibrillation	Unknown	Blood	Amoxicillin-clavulanic acid and piperacillin-tazobactam
Atas et al.[26]	2017	70/F	Peritonitis	CKD, dialisis	Unknown	Peritoneal fluid	Cefuroxime axetil and oral ciprofloxacin
Hee Lee et al.[27]	2017	74/M	Acute pyelonephritis	Diabetes mellitus	BacT/ALERT 3D Microbial Detection System (bioMerieux Inc., Durham)	Blood, Urine	Ceftriaxone
Gittemeier et al.[28]	2019	70/M	Aortic valve endocarditis	Diabetes mellitus type 2	MALDI-TOF MS	Blood	Vancomycin, ampicillin, ceftriaxone, penicillin G

BPH, benign prostatic hyperplasia; MALDI-TOF MS, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry. CKD: chronic kidney diseases. UTI: urinary tract infection.

improves local tumor NK cells, T cells, macrophages and dendritic cell responses in murine models of hepatocarcinoma. However, it is unclear whether these properties act in the same direction outside the tumor environment, because some of them (sunitinib and sorafenib) have been found to inhibit the activation, proliferation and production of cytokines in peripheral T cells of the blood.[13] These effects could potentially impact the response against some infections.

Likewise, therapy with sunitinib induced significant decreases in total leukocyte and neutrophil counts, as well as in certain peripheral blood lymphocyte subpopulations (total $CD3^+$ and $CD4^+$ subsets). These parameters return to baseline levels when sunitinib was discontinued.[13]

Recently, the European Medicines Agency (EMA) has approved regorafenib for the treatment of hepatocarcinoma, gastrointestinal stromal tumor, and metastatic colorectal carcinoma. This drug has potent receptor TKI activity targeted not only against VEGF but also against the angioprotein 1 receptor. Unlike previous VEGF TKI, regorafenib has not been associated with increased risk of infections in its pivotal phase III studies.[14] However, it should be noted that clinical experience accumulated with regorafenib is more limited so far.

This recent increase in TKI use opens a new field to explore in infectious diseases, as the increased risk of infections can be associated as well with pre-existing immunosuppression due to cancer and various comorbidities (diabetes mellitus, cirrhosis) that together with the use of new molecules that inhibit immune signaling pathways, may increase the risk of presenting an infection.

In our case, we cannot confirm that *E. hirae* infection was only due to the treatment with regorafenib, because our patient had immune suppression induced by other multiple pathologies (type 2 diabetes, COPD, chronic alcoholism, HCV cirrhosis).

In conclusion, in patients taking care or in close contact with birds, immunosuppressed by their underlying morbidities and under treatment with regorafenib, clinicians should be aware of an increased risk for unusual potentially severe infections.

Post-marketing surveillance seems warranted with these new VEGF TKI, and increased awareness of infectious disease specialists will be pivotal.

Conflicts of interest

The authors declare no conflicts of interest.

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