Sladana Pavić¹, Milena Branković², Dubravka Damljanović²,
Marija Antić¹, Irena Đurić¹

SEPSA IZAZVANA BAKTERIJOM *GRANULICATELLA SPECIES* – PRIKAZ SLUČAJA

Sažetak

Uvod: Bakterija *Granulicatella species* iz roda *Abiotrophia* poznata je kao nutritivna varijanta streptokoka. Normalno je stanovnik usne duplje, ali može uzrokovati invazivne infekcije, najčešće sepsu i bakterijski endokarditis, češće kod imunokompromitovanih osoba.

Cilj istraživanja je bio da prikazemo slučaj teške kliničke forme sepe i plućnog apscesa kod bolesnika kod koga je u serumu identifikovana *Granulicatella species*.

Prikaz slučaja

Tokom decembra 2016. na Odeljenju za infektivne i tropske bolesti Opšte bolnice u Užicu lečen je 59-godišnji muškarac. Primljen je na lečenje zbog febrilnosti, malaksalosti, zamora i ikterusa. U istoriji ranijih bolesti dobijen je podatak da ima hipertenziju i diabetes mellitus i da je prekomerno konzumirao alkohol. Pri prijemu je bio febrilan, ikteričan, dehidriran, uz auskultatorni patološki nalaz na plućima desno. U laboratorijskim nalazima uočena je leukocitoza uz povišen C reaktivni protein, trombocitopenija, hiperbilirubinemija, povišene vrednosti azotnih materija i hipoproteinemija uz povišene vrednosti serumskih transaminaza. Rentgenski snimak pluća i kompjuterizovana tomografija su ukazali na plućni apsces, a ultrazvuk abdomena na hepatosplenomegaliju. U hemokulturi je izolovana *Granulicatella species*. Lečen je kombinacijom antibiotika širokog spektra. Uprkos tome, u daljem toku bolesti došlo je do nastanka septičkog šoka i letalnog ishoda.

Zaključak: *Granulicatella species* normalno se može naći na mukoznim površinama gastrointestinalnog i urogenitalnog trakta. Pored toga, može izazvati teške invazivne infekcije. Lečenje takvih infekcija je teško, uz moguću smrtni ishod, posebno u slučaju drugih udruženih bolesti.

Ključne reči: *Granulicatella species*, sepsa, plućni apsces, komorbiditeti

¹ Sladjana Pavić, Odeljenje za infektivne i tropske bolesti Opšte bolnice Užice, Užice, Srbija, sladjanapj@gmail.com

² Mikrobiološka laboratorija Opšte bolnice Užice, Užice, Srbija

Uvod

Granulicatella species je bakterija iz roda *Abiothrophia*, odnosno nutritivna varijanta *Streptococcus species* (NVS). Normalni je stanovnik usne duplje, genitalnog i intestinalnog trakta (1). Nije među bakterijama koje se često izoluju u bolesničkom materijalu, ali može uzrokovati različite infekcije. U 5–6% seruma pacijenata sa streptokoknim endokarditisom izolovana je ova bakterija (2, 3). Nađena je i u sadržaju sinusa, oka, koštanoj srži, apscesima, uretri (4–7). Najčešće je opisana kao uzročnik endodontalnih infekcija i dentalnih apscesa (8, 9). U ređim slučajevima je izazvala osteomijelitis, pankreatitis, infekcije centralnog nervnog sistema, zglobova, kože i genitourinarnog trakta. Osim krvi, bakterija je izolovana i u drugom bolesničkom materijalu, kao što je gnoj, sinovijalna tečnost, ili uzorci tkiva (7, 10–13).

Cilj rada bio je da prikazemo težak klinički slučaj pacijenta sa sepsom i plućnim apscesom u čijoj je krvi identifikovana *Granulicatella species*.

Prikaz slučaja

Muškarac, star 59 godina, primljen je na Odeljenje za infektivne i tropske bolesti Opšte bolnice Užice zbog malaksalosti, zamora, visoke telesne temperature (39°C) i žute prebojenosti kože i beonjača. Pet godina ranije imao je operaciju perforiranog duodenalnog ulkusa. Sedam godina unazad redovno je uzimao lekove za hipertenziju i primao insulin zbog diabetes mellitus-a. Nije pušio cigarete, ali je svakodnevno prekomerno konzumirao alkohol.

Pri prijemu je bio svestan, orijentisan, febrilan (38.5°C), ikteričnih sklera i kože, dehidriran i kardijalno kompenzovan. Nije bilo znakova manifestnog krvarenja. Auskultatorni disajni zvuk na plućima je bio oslabljen desno bazalno uz prisutne kasno-inspirijumske pukote. Auskultatorni nalaz na srcu je bio u fiziološkim granicama, puls 73/min, krvni pritisak 120/80 mmHg. Abdomen je bio normalnog kliničkog nalaza, jetra i slezina palpatorno nisu bile uvećane.

U tabeli 1. prikazani su laboratorijski nalazi našeg pacijenta.

Tabela 1. Laboratorijski parametri bolesnika sa sepsom čiji je uzročnik *Granulicatella species*

Laboratorijska analiza (normalna vrednost)	Vrednost pri prijemu
WBC (3.4 – 9.7x10 ⁹ /L)	18.6
RBC (3.8 – 5.7x10 ¹² /L)	2.9
Hb (11.9 – 17.8 g/dL)	10.7
PLT (150 – 450x10 ⁹ /L)	88
Glikemija (4.1 – 5.9 mmol/L)	15.2

Urea (3.2 – 8.2 mmol/L)	25.3
Kreatinin (44.2 – 97.2 μ mol/L)	202.9
Albumini (35 – 52 g/L)	30
Bilirubin ukupni (5.1 – 17.0 mmol/L)	141
direktni (1.0 – 5.0 μ mol/L)	96
AST (< 34 U/L)	124
ALT (10 – 49 U/L)	95
GGT (< 40 U/L)	224
C reaktivni protein (< 10 mg/L)	313

Rentgenski snimak pluća ukazao je na eleviranu levu hemidijafragmu sa apscesnom promenom u donjem režnju levog plućnog krila. Kompjuterizovanom tomografijom grudnog koša opisana je apscesna promena promera 38x44mm uz prisustvo uvećanih medijastinalnih limfnih žlezda. Abdominalnim ultrazvukom viđena je hepatosplenomegalija i manja količina ascitesa. U hemokulturi je izolovana *Granulicatella species*. Za izolaciju bakterije korišćene su preporučene standardne metode (14).

Odmah je započeta opšta, simptomatska i antibiotska terapija. U početku je pacijent lečen ceftriaksonom, a zatim meropenemom i vankomicinom. Pacijent je primao albumine, diuretike, insulinsku i hepatoprotektivnu terapiju. Redovno je rađen dnevni profil glikemije i praćena diureza. Konsultovan je torakalni hirurg koji nije postavio indikacije za operativno lečenje plućnog apscesa. I pored svega primenjenog, nažalost, došlo je do nastanka septičkog šoka. Bolest se završila letalnim ishodom šestog dana bolesti.

Diskusija

Infekcije kojima je etiološki uzročnik *Granulicatella species* mogu varirati od lakih do izuzetno teških. Opisan je smrtni ishod u 9% bolesnika (7). Najčešće ozbiljne kliničke forme su endokarditisi (15). Naš pacijent sa apscesom pluća nastalim zbog *Granulicatellae species* redak je primer takve infekcije ovom bakterijom i bez dostupnih sličnih primera u literaturi.

Apsces pluća predstavlja nekrozu plućnog tkiva i stvaranje šupljina koje sadrže nekrotične supstance, a najčešće nastaje usled infekcije. Izvor bakterije kod našeg pacijenta nije bilo moguće dokazati. Nije prethodno bio izložen invazivnim dijagnostičkim procedurama, niti je imao ugradnju proteza ili implantata. Jedina invazivna svakodnevna terapijska mera bilo je supkutano davanje insulina. Detaljnim pregledom nije uočena vidljiva infekcija kože, ili mekih tkiva koja bi bila izvor infekcije.

Međutim, plućni apscesi mogu nastati i nakon aspiracije sekreta iz usta kod pacijenata sa gingivitisom, ili lošom higijenom usne šupljine. Ovo se obično događa kod osoba koje su iz nekog razloga u besvesnom stanju. Do takvog stanja može dovesti predoziranje lekovima, davanje anestetika, sedativa ili uzimanje opijata. Mogući uzrok aspiracije orofaringealnog sekreta u kome se nalazi *Granulicatella* može biti alkoholizirano stanje. Heteroanamnestički podaci najbliže rodbine našeg pacijenta ukazali su na svakodnevno prekomerno konzumiranje alkohola. Zbog toga je bio povremeno dezorijentisan i somnolentan. U takvom stanju je, po našem mišljenju, moglo doći do aspiracije orofaringealnog sekreta i posledičnog nastanka apscesa u plućima. U ovoj patogenezi apsces bi bio izvor bakterije i nastanka sepsa.

Punkcija apscesa i uzimanje sadržaja za mikrobiološku analizu bila bi od velikog dijagnostičkog značaja, ali, po mišljenju hirurga, nije bila izvodljiva zbog nepostojanja tehničkih uslova za ciljanu biopsiju.

Iako je odmah započeta antibiotska terapija i uprkos antibiogramu koji je ukazao da je bakterija bila osetljiva na primenu antibiotike, kod našeg pacijenta je došlo do progresije bolesti i razvoja septičkog šoka. I u slučaju drugih infekcija izazvanih ovom bakterijom bilo je letalnih ishoda (16). Pogoršanje bolesti sigurno su doprinele ranije udružene bolesti – alkohola, bolest jetre i diabetes mellitus. Bolesnik je pri prijemu imao i akutna, bubrežnu insuficijenciju, ali je bubrežna funkcija normalizovana trećeg dana lečenja. Prilikom poslednje kontrole, mesec dana ranije, u laboratorijskim nalazima našeg pacijenta bila je prisutna laka trombocitopenija, bez anemije i hipoproteinemije, uz lako povišene transaminaze i vrednosti bilirubina u fiziološkim granicama. Nalazi pri prijemu mogli bi odgovarati dijagnostikovanom septičnom stanju. Međutim, intenzivno konzumiranje alkohola danima pre prijema svakako je doprinelo i kliničkom stanju i prikazanim laboratorijskim nalazima.

Prisutna mala količina ascitesa shvaćena je kao komplikacija alkoholne bolesti jetre. U literaturi je opisan slučaj spontanog bakterijskog peritonitisa izazvanog *Granulicatellom* koja je kultivisana iz ascitesa (17). Bilo bi interesantno ispitivanje ascitesa našeg pacijenta na prisustvo ove bakterije. Pomenuta dijagnostička metoda nije planirana pošto se radilo o maloj količini slobodne tečnosti u abdomenu koja nije izazivala tegobe.

Zaključak

NVS infekcije i u doba moderne medicine predstavljaju dijagnostičke i terapijske izazove. Nema dovoljno velikih kliničkih studija, pa je naše znanje zasnovano na malom broju opisanih slučajeva. Iako je *Granulicatella species* stanovnik normalne flore ljudskog organizma, potrebno je u kliničkom radu obratiti pažnju na patogeni potencijal ove bakterije. Kod osoba sa komorbiditetima ona može izazvati infekcije sa teškom kliničkom slikom i letalnim ishodom.

Sladana Pavić¹, Milena Branković², Dubravka Damljanović²,
Marija Antić¹, Irena Đurić¹

SEPSIS PER *GRANULICATELLA SPECIES* – A CASE REPORT

Abstract

Introduction: *Granulicatella species*, the genus *Abiotrophia*, were originally known as nutritionally variant streptococci. They are a normal component of the oral flora, but can be the cause of invasive infections, like sepsis, bacterial endocarditis, more often in immunodeficiency persons.

The aim of the study was to present a case of severe clinical form of sepsis and pulmonary abscess in a patient with *Granulicatella species* in the serum.

Case Outline: A 59-year-old man, was treated on Department for Infectious and Tropical Diseases, General Hospital Užice, in December 2016. He felt weakness, fatigue, had jaundice and fever.

Patient's history included diabetes mellitus and excessive consumption of alcohol. On admission, he was febrile, icteric, dehydrated, with auscultation pathology on the right lung. In laboratory findings was leukocytosis, elevated C reactive protein, thrombocytopenia, hyperbilirubinemia, elevated nitrogen levels, hypoproteinemia and elevated serum transaminases. Lung X-ray and computed tomography indicated pulmonary abscess. Abdominal ultrasound showed hepatosplenomegaly and small ascites *Granulicatella species* was isolated in hemoculture. Patient was treated with a combination of broad-spectrum antibiotics. Despite this, the onset of the disease resulted in septic shock and a lethal outcome.

Conclusion: *Granulicatella species* is normally on the mucous surfaces of the gastrointestinal and urogenital tract. In addition, it can cause severe invasive infections. Treating such infections is difficult. In people with comorbidities, a fatal outcome is possible.

Key words: *Granulicatella species*, sepsis, pulmonary abscess, comorbidities

¹ Sladjana Pavić, Odeljenje za infektivne i tropske bolesti Opšte bolnice Užice, Užice, Srbija, sladjanapj@gmail.com

² Mikrobiološka laboratorija Opšte bolnice Užice, Užice, Srbija

Introduction

Granulicatella species is a bacterium of the genus *Abiothrophia*, the nutritional variant of *Streptococcus species* (NVS). He is a normal resident of the oral, genital and intestinal tract (1). This bacteria is not often isolated in patient material, but it can cause various infections. *Granulicatella* was isolated in 5-6% of sera of patients with streptococcal endocarditis (2, 3). It has also been found in the contents of the sinus, eye, bone marrow, abscesses, urethra (4–7). *Granulicatella* is most commonly described as the cause of endodontic infections and dental abscesses (8, 9). This bacteria has caused osteomyelitis, pancreatitis, central nervous system infections, joints, skin and genitourinary tract, in rare cases. *Granulicatella species* was isolated in other patient material, such as pus, synovial fluid, or tissue samples (7, 10–13).

The aim of this study was to present a severe clinical case of a patient with sepsis and pulmonary abscess with *Granulicatella species* in the blood.

Case report

A 59-year-old man was admitted to the Department of Infectious and Tropical Diseases, General Hospital Uzice due to nausea, fatigue, high body temperature (39 °C) and jaundice. He had surgery for a perforated duodenal ulcer five years ago. He has been regularly taking antihypertensive medications and receiving insulin for seven years. He did not smoke cigarettes, but he over-consumed alcohol.

On admission, he was conscious, oriented, febrile (38.5 °C), icteric sclera and skin, dehydrated and cardiac compensated. There were no signs of manifest bleeding. The breathing sound was dull with late-inspiratory cracks. The auscultation heart rate was within physiological limits, pulse 73/min, blood pressure 120/80 mmHg. The abdomen was a normal clinical finding, the liver and spleen were not enlarged. Our patient's laboratory findings are shown in Table 1.

Table 1. Laboratory parameters of patients with sepsis-induced *Granulicatella species*

Laboratory analysis (normal)	Value at hospital admission
WBC (3.4 – 9.7x10 ⁹ /L)	18.6
RBC (3.8 – 5.7x10 ¹² /L)	2.9
Hb (11.9 – 17.8 g/dL)	10.7
PLT (150 – 450x10 ⁹ /L)	88
Glycemia (4.1 – 5.9 mmol/L)	15.2

Urea (3.2 – 8.2 mmol/L)	25.3
Creatinine (44.2 – 97.2 μ mol/L)	202.9
Albumins (35 – 52 g/L)	30
Bilirubin total (5.1 – 17.0 mmol/L) conjugated (1.0 – 5.0 μ mol/L)	141 96
AST (< 34 U/L)	124
ALT (10 – 49 U/L)	95
GGT (< 40 U/L)	224
C reactive protein (< 10 mg/L)	313

An X-ray of the lung indicated an elevated left hemidiaphragm with an abscess in the lower lobe of the left lung. Computed tomography (CT) of the chest describes an abscess 38x44mm diameter and enlarged mediastinal lymph glands. Abdominal ultrasound showed hepatosplenomegaly and a small ascites. *Granulicatella species* was isolated in hemoculture. The recommended standard methods have been used for bacterial isolation (14).

Antibiotic and symptomatic therapy was started immediately. He was initially treated with ceftriaxone, followed by meropenem and vancomycin. The patient received albumin, diuretics, insulin and hepatoprotective therapy. The daily glycemic profile and diuresis were monitored regularly. A thoracic surgeon was consulted who did not indicate surgical treatment of pulmonary abscess. Despite all that was applied, unfortunately, there was a development of septic shock. The disease ended with the lethal outcome of the sixth day of illness.

Discussion

Infections caused by *Granulicatella species* can range from light to extremely heavy. Death in 9% of patients has been reported (7). The most common serious clinical forms are endocarditis (15). Our patient with a lung abscess caused by *Granulicatellae species* is a rare example of infection with this bacterium and without similar examples available in the literature.

Lung abscess is a necrosis of the lung tissue and the formation of cavities containing necrotic systems, most often caused by infection. The source of the bacteria in our patient could not be proven. He had not previously been exposed to invasive diagnostic procedures, prosthesis or implants. The only invasive daily therapeutic measure was subcutaneous insulin delivery. Clinical examination did not identify any visible skin or soft tissue infection that would be the source of the infection.

However, pulmonary abscess can also occur after aspiration of oral secretions in patients with gingivitis or poor oral hygiene. This usually happens in patients who are unconscious. This can be caused by drug overdose, administration of anesthetics, sedatives, or opiate use. A possible cause of aspiration of the oropharyngeal secretion containing *Granulicatella* may be an alcoholic condition. Hetero-anamnestic data from our patient's closest relatives indicated daily excessive alcohol consumption. As a result, the patient was occasionally disoriented and somnolent. In this condition, in our opinion, aspiration of the oropharyngeal secretion and consequent abscessus in the lungs could have occurred. In this pathogenesis, an abscess would be a source of bacteria and sepsis.

Puncturing the abscess and taking the contents for microbiological analysis would be of great diagnostic importance, but, in the surgeon's view, it was not possible due to the lack of technical conditions for targeted biopsy.

Antibiotic therapy was started immediately and an antibiogram indicating that the bacterium was sensitive to antibiotic administration. Despite everything, our patient experienced disease progression and septic shock. The disease was fatal. There were also lethal outcomes in the case of other *Granulicatella* infections (16). The exacerbation of the disease was certainly compounded by previously associated diseases - alcohol liver disease and diabetes mellitus. The patient also had acute renal failure at admission, but renal function was normalized on the third day of treatment. At the last control, one month earlier, mild thrombocytopenia was present in the laboratory findings of our patient, without anemia and hypoproteinemia, with easily elevated transaminases. Admission findings may be due to sepsis. However, intense alcohol consumption in the days before admission certainly contributed to both, the clinical condition and the laboratory findings.

The small ascites could be a complication of alcoholic liver disease. The case of spontaneous bacterial peritonitis caused by *Granulicatella* has been reported in the literature (17). It would be interesting to examine our patient's ascites for the presence of this bacteria. This diagnostic method was not planned since it was a small amount of free fluid in the abdomen that did not cause any problems.

Conclusion

NVS infections, present diagnostic and therapeutic challenges, even in the age of modern medicine. There are not enough large clinical studies, so our knowledge is based on the small number of cases described. Although *Granulicatella species* is a resident of the normal flora of the human body, it is necessary to pay attention to the pathogenic potential of this bacteria. In people with comorbidities, it can cause infections with severe clinical imaging and lethal outcome.

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