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Case Report Open Access

Nocardiosis in a Patient with Acute Necrotizing Pancreatitis. Can A Simple Microscope Specimen Save a Patient's Life? A Case Report

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Abstract

Objective: A 50-year-old immunocompetent patient was hospitalized following an episode of acute necrotizing pancreatitis. Piperacillin/tazobactam was administered empirically. Despite continuous IV antibiotic therapy, on the 20th day of treatment the patient required urgent laparotomy. A swab sample was collected and subsequent Vancomycin with Amikacin administered empirically.

Design: Despite administration of intensive treatment, general clinical condition of the patient deteriorated. The question was, why we experienced ineffectiveness of conservative treatment, as well as of subsequent surgical procedures? Was the microbiological specimen taken incorrectly? Why was it difficult to identify bacteria constituting the etiological infection source?

Results: What is emphasized in our article is the significance of proper collection of a specimen and gathering an appropriate clinical history. What also needs to be taken into account in severe acute pancreatitis is perhaps allowing for longer bacterial culture growth.

Conclusion: In this case, the infection was caused by a past injury with the previously undiagnosed etiological factor, i.e. Nocardia spp., challenging both current diagnosis and treatment, which ultimately resulted in severe necrotizing pancreatitis. This indicates the importance of a microbiologist for diagnosis and treatment.

Keywords: Nocardiosis; Nocardia spp; Acute pancreatitis; Pancreatic abscess; Necrotizing pancreatitis

Case Report

A 50-year-old patient was admitted due to increasing abdominal pain accompanied with nausea and vomiting. Prior to admission the patient developed discomfort in the epigastric region which was accompanied by nausea. In the evening, the patient's general condition deteriorated as persistent pain appeared together with vomiting with no relief. The pain increased significantly, the patient vomited several times, was weak, and it was more difficult to maintain logical contact with him. On admission blood pressure was 160/90, pulse 115 beats/min., saturation 97%, tachypnea (24 breaths/min.). Laboratory results presented glycaemia 221 mg/dl, CRP 6.5 mg/dl, serum amylase 722 U/l and a slight anemia with Hb 13.3 g/dl.

His medical history revealed cholecystectomy, stable angina pectoris, type 2 diabetes, hypertension. The patient was continued on betaxolol, ramipril, torasamide, rosuvastatin, fenofibrate, trimetazidine, and metformin. He did not report any allergies, had not been smoking for several years, and used nicotine substitutes only periodically. He did not consume alcohol.

The patient was classified as risk group 2 due to diabetes, obesity, and hospitalization within the last 12 months. Other risk factors were dismissed by the patient.

On admission the patient was conscious and oriented to time, place, and person. On examination type I obesity was observed with BMI 32.5, blood pressure 160/90, pulse 115 beats/min., body temperature 36.8°C, saturation 97%. The abdomen was soft, distended, tender in the epigastric region, negative peritoneal signs, slow peristalsis, with no pathological resistance. On auscultation, symmetric alveolar murmur was observed, although percussion did not indicate any changes. Other general and neurological tests showed no significant deviations from the norm (Table 1), with the APACHE II score equal to 12 points.

Abdominal X-ray showed no pathological changes. Chest X-ray revealed only high positioning of the left diaphragm dome. During abdominal USG examination hepatic steatosis was confirmed. No free fluids in the abdominal cavity were discovered, and the pancreas was covered by intestinal gasses.

In differential diagnosis the following conditions were considered: acute pancreatitis, cholelithiasis, perforation and digestive tract obstruction, abdominal aorta aneurysm, intestinal ischemia, and myocardial infarction.

Due to the diagnosed acute pancreatitis, the standard conservative treatment was ordered. The patient received multi-electrolyte fluid and 0.9% NaCl 250 ml/hr, analgesics (paracetamol, pethidine, metamizole), proton pump inhibitors and anticoagulation prophylaxis according to the Caprini risk assessment model. The patient also underwent a daily urine collection, circulatory system monitoring and fasting. On the 3rd day, CT scan of the abdominal cavity was performed in order to assess the presence of necrosis. As a result, hypoperfusion and a small amount of fluid were discovered. On the 4th day enteral nutrition was attempted via naso-intestinal probe; however, due to the patient's intolerance it was removed and parenteral nutrition was reintroduced. On the 7th day CT scan was performed again and piperacillin/tazobactam was administered empirically since the patient's general condition deteriorated. According to APACHE II, score reassessment was 13 (Table 1). Furthermore, control CT scan demonstrated a faint

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	0. day	7th day	20th day	22nd day	50th day	60th day
WBC	10.20 × 10^3/µl [3.90 – 11.00]	13.10 × 10^3/µl	10.90 × 10^3/µl	17.50 × 10^3/µl	9.0 × 10^3/µl	6.0 × 10^3/µl
RBC	4.39 × 10^6/µl [4.20-5.80]	3.21 × 10^6/µl	2.95 × 10^6/µl	3.68 × 10^6/µl	3.29 × 10^6/µl	3.76 × 10^6/µl
Hb	13.3 g/dl [13.5-17.2]	9.5 g/dl	8.7 g/dl	10.6 g/dl	9.0 g/dl	10.5 g/dl
HCT	38.5% [39.5-50.5]	28.1%	26.9%	32.5%	27.6%	31.9%
PLT	275 × 10^3/µl [130-400]	330 × 10^3/µl	461 × 10^3/µl	635 × 10^3/µl	551 × 10^3/µl	446 × 10^3/µl
Sodium	141 mmol/l [136-145]	139 mmol/l	133 mmol/l	130 mmol/l	132 mmol/l	138 mmol/l
Potassium	4.30 mmol/l [3.50-5.10]	3.33 mmol/l	3.80 mmol/l	4.38 mmol/l	4.89 mmol/l	4.30 mmol/l
Creatinine	0.98 mg/dl [0.70-1.20]	0.60 mg/dl	0.78 mg/dl	1.56 mg/dl	0.65 mg/dl	0.61 mg/dl
GFR	eGFR according to MDRD: above 60 ml/ min/1.73 m^2 [>60]	eGFR according to MDRD: above 60 ml/ min/1.73 m^2 [>60]	eGFR according to MDRD: above 60 ml/ min/1.73 m^2 [>60]	eGFR according to MDRD: 47 ml/ min/1.73 m^2 [>60]	eGFR according to MDRD: above 60 ml/ min/1.73 m^2 [>60]	eGFR according to MDRD: above 60 ml/ min/1.73 m^2 [>60]
CRP	CRP: 6.5 mg/l [<5.0]	460.4 mg/l	184.0 mg/l	292.5 mg/l	61.2 mg/l	12.5 mg/l
GLU	221 mg/dl [70-99 (fasting)]		245 mg/dl	157 mg/dl	180 mg/dl	114 mg/dl
Amylase	722 U/l [28-100]		279 U/l	348 U/l	80 U/l	
Troponin	<3 ng/l [=/<14 ng/l (99 percentile URL at CV<10%)]					
APACHE II Score		13	13	18	9	7

Table 1: Other general and neurological tests showed no significant deviations from the norm.

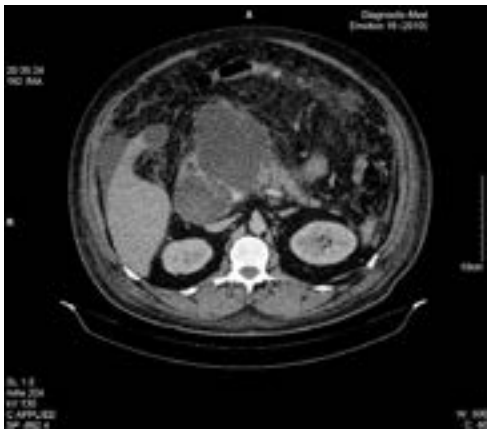

Figure 1: Necrotising pancreatitis with acute necrotic collections.

pancreas structure, free fluid around it, as well as an infiltration of the peripancreatic adipose tissue. On the 14th day, the patient complained of dyspnea at rest with numerous crepitations over the upper lobes. Increasing diffuse edema in the lower extremities and genitalia was noted. Additionally, the patient's level of pain increased. Intensive edema treatment with negative water balance was introduced with good outcome. As a result, CRP level started to decrease; however, constant opioid administration was necessary due to intolerable pain. On the 20th day, antibiotics were discontinued and the dosage of analgesics was reduced. After 2 days, a sudden deterioration occurred with an intensified pain and an increased CRP level. During control CT scan an abscess in the left hepatic lobe was discovered (200 × 140 mm), additionally one in the hepatic hilum (108 × 96 mm), with numerous smaller abscess' located in the interloop area (Figure 1). Having confirmed the vast necrotic areas of the pancreas, the patient was qualified for laparotomy. Necrosectomy with peritoneal toilet and drainage were performed. Additionally, samples from the pancreas were taken for the histopathological examination. Due to small volume of pus specimen, a single swab sample was collected for microbiology tests. Consecutively, vancomycin was administered empirically 1.0 g 3×/day i.v. and amikacin 1.0 g 3×/day i.v. Further laparotomic surgeries were performed with peritoneal toilet and draining implemented on the 2nd and 5th day after the surgery. Nevertheless, microbiology cultures from three previous surgeries were sterile. On the 13th day control CT scan revealed an abscess 130 × 50 mm on the anterior stomach wall, as well as in the subdiaphragmatic area – 53 × 17 mm. During operation 50ml of pus was collected from a large abscess. In the direct specimen Nocardia spp. was discovered, although the bacteria was impossible to grow in spite of a 2-week-long culture time. The pathology report of the histopathological samples described only necrotizing tissue. After empirical administration of the first-line antibiotic recommended in nocardiosis (trimethoprim/sulfamethoxazole), a gradual improvement of the general condition was observed (Table 1). Trimethoprim/ sulfamethoxazole was administered 960 mg 2×/day i.v. As a result, a steady decrease in CRP and WBC was observed. Additionally, the dosage of analgesics was gradually reduced until they were discontinued. In the control tests a gradually decreasing fluid collection was observed. The patient underwent rehabilitation with good effects, and parenteral nutrition was ceased. Chest and head CT scan were performed in order to assess the presence of secondary abscesses, which were excluded. On the 60th day the patient was discharged from the hospital in good condition. The patient was monitored in the outpatient clinic for the subsequent two months. During imaging examination, further decrease in fluid collection was observed. The patient underwent a 6-month-long treatment with Biseptol in the following pattern: 4 weeks 2 × 960 mg, then 20 weeks 2 × 480 mg. Additionally, in the outpatient department fiber colonoscopy was performed in order to confirm non-specific inflammation proctitis and sigmoid diverticulitis were confirmed.

Discussion

20 to 70 cases of acute pancreatitis per 100000 inhabitants are noted in Poland each year [1]. In 5-10% of cases necrosis appears within the first days and becomes infected in 16-47% patients [2-4]. It constitutes one of the most serious complications with mortality reaching 30% [5,6]. The inflammation is connected with bacteria translocation to the blood and consecutively to the pancreas. It is a multifactor aspect which combines decrease in the peristalsis, damage to the intestinal mucous membrane lining due to ischemia, and immunity decline. Usually, it is possible to grow bacteria constituting intestinal flora. For this reason,

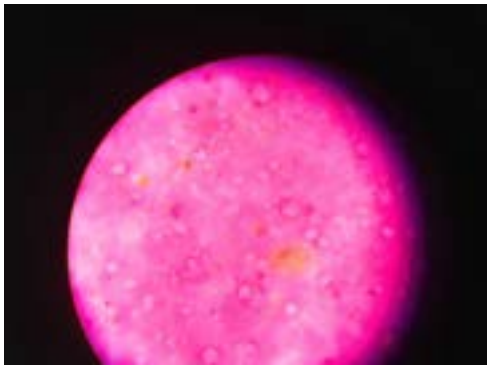

Figure 2: Gram Stain of *Nocardia spp.* in abdominal abscess.

in the reported case piperacillin/tazobactam was administered empirically which is frequently used against intestinal bacteria. In the case in question, blood was sterile after a course of antibiotics employed beforehand.

Despite microbiological samples collected routinely during each of the patient's five surgical procedures, a positive result was found only on the fourth procedure, yielding Nocardia spp. This may have been due to the volume insufficiency of the specimens collected on swabs, since Nocardia spp. are usually present in small numbers and may hence give false negative results [7]. During the fourth specimen collection, liquid pus was taken and microscope specimen was prepared. The goal of the paper is to emphasize how crucial a microscope specimen is in the diagnostic and therapeutic process. On the basis of recommendations, every microbiological laboratory prepares specimens from collected pus, requiring two swabs: one for culture, the other for the specimen. In our case, only one swab was collected due to the low presence of pus despite a large necrotic area found in the patient's three previous surgical procedures. The result was negative. Taking into the account that Nocardia spp. are slow-growing organisms in a routine diagnostic process, if a positive culture does not appear during 48-72 hours, the result is negative. This could be the explanation for our negative result.

During the 4th procedure, pus was collected in a sterile container. In this case, the laboratory prepared the direct specimen treated with Gram's staining method, in accordance to the regulations [8]. Thread-like branching bacteria was present in the specimen (Figure 2), as evidenced in literature [8]. Moreover, the picture of our specimen is included. Due to the absence of any epidemiological hints suggesting tuberculosis, typical image in the direct microscopy, fast response to trimethoprim/sulfamethoxazole, the laboratory did not perform any additional stains, like Ziehl-Neelsen stain. From the epidemiological point of view, growth of bacteria on Lowenstein-Jensen slant is being done in the tuberculosis reference laboratory. In addition, Nocardia spp. are aerobe bacteria [7] and therefore, they are rarely taken into account as the etiological bacteria in abscess formation which is most frequently connected with anaerobe bacteria.

Nocardiosis most commonly affects the lungs and skin, and physical injury is often the primary source of infection. It may spread to other tissues like kidneys and brain tissue [9,10]. In 45% of lung nocardiosis, the infection spreads via the blood into various locations – 3% appearing in liver. Another case was described in literature in which Nocardia spp. infection was associated with a car accident originally affecting the lungs [11]. In our presented case report, the infection involved the abdomen, therefore, it is considered a secondary infection. Initially, the portal of entry was investigated. Since on admission the patient did not report any pulmonary or skin symptoms, it was suggested that a past injury along with contact with soil may have accounted for the presence of Nocardia spp. in the specimen. This species of bacteria are present in the natural environment - in the soil, water and air [8]. Hence, all human infections caused by Nocardia spp. are extrinsic [7,12]. In the reported case, there was a history of a hallux abscess, occuring one year before the current hospitalization. It was the result of injury by an animal bone while working in the garden. Since the lesion healed by pus eruption and emptying of its contents, the patient did not consult the doctor. Furthermore, nocardiosis most often appears in patients with decreased immunity [9], although it may develop also in healthy subjects. The patient in question, prior to hospitalization, was under massive stress due to his twin brother's death. Additionally, he was an obese diabetic which further decreased his immunity.

On the basis of Nocardia spp. in the specimen, the recommended treatment of choice in nocardiosis was ordered, i.e. trimethoprim/sulfamethoxazole [8,13]. Since Nocardia spp. is a difficult bacteria to culture, therefore making it impossible to obtain an antibiogram, the majority of nocardiosis cases are treated empirically [14]. Nevertheless, cases resistant to sulphonamides may appear [15]. Linezolid is also considered to be an appropriate drug for nocardiosis treatment, but clinical data is very scarce. In fact, a case of lung nocardiosis was described where trimethoprim/sulfamethoxazole therapy failed after 5 months. In our patient after treatment with this antibiotic, the patient's condition improved. Despite bacterial culture, performed alongside the specimen and lengthening the incubation time up to 2 weeks, it was impossible to grow these bacteria. It may have occurred due to the previously given recommended course of antibiotic which, on one hand, did not present any clinical effect, and ,on the other, it weakened the bacterium so that no in vitro culture growth was observed. Initially, while the Nocardia spp. infection had not been yet properly diagnosed, the patient was on piperacillin/tazobactam. There are no cases in literature concerning the efficacy of this drug in nocardiosis treatment. Perhaps the period of administration was not long enough? After its discontinuation in our patient, amikacin and vancomycin were introduced. One piece of literature presented a finding that 100% of bacteria strains are susceptible to amikacin, whereas Nocardia spp. are usually vancomycin resistant [11]. Vancomycin showed no results in our patient and amikacin was ineffective in monotherapy, or was administered incorrectly compared to guidelines. The therapeutic effect depends on its concentration and thus, has to be administered once daily at a full dose. In order to achieve therapeutic success, the administered drugs are equally as important as dosage and therapy length. Depending on the patient's clinical state, nocardiosis treatment duration is 6-12 months [7].

Nocardiosis constitutes an extremely rare and diagnostically challenging disease and described cases are sporadic [7]. The cooperation between the clinicians and microbiologists is vital because on the basis of clinicians' recommendations and suggestions, it will be possible to prolong culture incubation time. By doing so this allows a more specific results, thus obtaining expected clinical results.

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