Journal of Clinical Infectious Disease and Practice

Barry et al., J Clin Infect Dis Pract 2021, 6:2
DOI: 10.4172/2476-213X.1000134

Case Report Open Access

New Delhi Metallo- β -Lactamase 1 (NDM 1) *Klebsiella Pneumoniae* in Saudi Arabia First Case the Report and Literature Review

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Received date: March 08, 2021; **Accepted date:** March 22, 2021 ; **Published date:** March 29, 2021

Case

Our patient is a 56 years old Indian gentleman who presented to our hospital's emergency department with right upper quadrant pain which started three hours earlier, the pain was colicky and moderately severe, there was none of the following: radiation, nausea, vomiting, fever nor jaundice. He was hemodynamically stable, on physical exam he had mild tenderness over the right upper quadrant, no guarding nor rigidity, bowel sounds were audible, liver function tests were sent and all the enzymes and bilirubin were within normal range. No ultrasound was done at this time; he was given intramuscular scopolamine, and was prescribed ranitidine daily. He remained symptom free for the next 4 months, when he developed sudden onset of fever, chills and rigors, with no other symptoms, he again presented to our hospital's emergency department, the emergency physician's assessment couldn't find a focus of infection for his fever, a blood culture was drawn, and he was discharged on acetaminophen. That same night the blood culture grew a gram negative *bacilli*, he was called back to the emergency department, where intravenous ceftriaxone was started, the gram negative was later identified as *E. coli*, which was an extended spectrum β Lactamase (ESBL) producer, it was only susceptible to imipenem. Despite that he was continued for five days on the ceftriaxone. Two days after it was stopped he developed right upper quadrant pain again with nausea, vomiting, and fever, physical exam showed temperature 38.3˚C, heart rate 113 bpm, blood pressure 134/72 mm Hg, his abdominal exam showed a tender right upper quadrant with positive murphy's sign, remaining abdomen was non tender, and abdominal sounds were audible in all four quadrants. A complete blood count showed a white cell count of 37 with a left shift and toxic changes, his bilirubin was 20 umol/L, Alkaline phophatase 111 U/L, Alanine aminotransferase 36 U/L. Abdominal ultrasound sowed evidence of acute cholecystitis, with a two centimeter stone at the neck of the gall bladder. He was admitted to the hospital, piperacillin tazobactam was started intravenously, the same day he underwent a laproscopic cholecystectomy, empyema was seen during procedure and a Gall Bed bed drain was placed, which had only minimal drainage of 40 ml of bile on the first post-operative day, the culture of the drain fluid did not grow any organisms. During his hospital stay he had no fevers, his pain resolved, and on the fifth post-operative day he drained only 14 ml of bile, it was then removed and the piperacillin tazobactam was stopped, he was discharged the same day without medications. Three days later he came back to the emergency room with fever, urgency, and dysurea, urinalysis showed nitrites positive and many bacteria, no culture was sent. His white cell count was 23 with a left shift, an ultrasound of the gall bladder surgical bed showed a small area with clear free fluid 1 by 1 cm, but no subphrenic collection, and intraheptic biliary system appeared normal, he was prescribed ciprofloxacin and sent home.

The next day he travelled to Hyderabad India, he continued to have fever so he visited a hospital there where an ultrasound was performed and showed post cholecystectomy status with well-defined fluid collection in gallbladder with air pockets, CT scan confirmed presence of an abscess, he was admitted there and underwent urgent percutaneous drainage; 100 ml of pus was drained, then the fever subsided, and a drain was left, the fluid grew an ESBL *E. coli* susceptible to carbapenems, gentamicin and tigecycline. The ciprofloxacin was stopped and was placed on imipenem. also during his hospitalization he underwent ERCP with placement of a stent which was removed two days later. He stayed in hospital for 8 days then discharged with the drain and was symptom free, he was discharged on faropenem orally for 7 more days, at that point he returned to have the drain removed as it was only draining 10 ml per day. Two days later he developed fever with chills and rigors, at that point he travelled back to Riyadh, Saudi Arabia, presented to the general surgery clinic, an ultrasound was done and showed a 30 ml collection at the gall bladder bed site, a cystic leak was suspected, he was admitted to the hospital and a drain was placed, 30 ml of clear fluid was removed. The gram stain of the fluid didn't show any organisms but the culture grew *Klebsiella Pneumoniae* which was only susceptible to amikacin, colistin, and tigecycline, which was later identified to be NDM-1, an infectious diseases consultation was requested, subsequently he was started on amikacin, and placed on contact isolation. He continued to drain 15-30 ml daily, and remained symptom free, his creatinine was stable and the amikacin pre level was 1.7 mcg/mc and post level was 21.8 mcg/ml. Two weeks later he developed recurrence of the right upper quadrant pain, no other symptoms, no fever. Ultrasound was done and showed a 2.4 cm × 2 cm collection near the gall bladder bed and a small fossa stone. He was then taken to the operating theatre and underwent laproscopic hand assisted retrieval of impacted cystic duct stone: there was a subhepatic fluid collection, drained, with drain left inside. The fluid grew *E. coli* ESBL which was amikacin resistant. Imipenem was started in addition to amikacin, over next two weeks his symptoms resolved, and the drainage stopped, a repeat ultrasound showed a small 1 cm by 1 cm collection. He was continued on the antibiotics for one more week and was discharged for a follow up the next week. He remained asymptomatic after discharge.

His past medical history includes dyslipidemia, Bell's palsy two years ago, duodenal ulcer due to *H. Pylori* 13 years ago, hemorrhoids 14 years ago, mild deafness he requires a left hearing aid, has history of latent tuberculosis that was treated 15 years ago. He does not consume

alcohol, he is a smoker for 25 years, his only medication is gemfibrozil, he has no known drug allergies, and he lives in Riyadh for the past 50 years moving from India as a child, he frequently visits India. He works as a library clerk. He has no animal contacts.

Laboratory method

Identification of organism and susceptibility testing were carried out by the MicroScan Walkaway 96 plus System (Siemen Healthcare Diagnostic Inc. Deerfield, IL). The minimum inhibitory concentration (MIC) for the following antibiotics; imipenem, meropenem, ertapenem, colistin and tigecycline were determined by the E-test (AB Biodisk, solna, Sweden) following the manufacturer's instructions and results interpreted according to clinical breakpoints from the CLSI. Disk diffusion susceptibility test was also carried out on Mueller Hinton agar and zone of inhibition results interpreted according to CLSI guidelines. The method currently endorsed by the CLSI for confirmation of production of carbapenemase is the modified Hodge test. In this test a disk containing imipenem was placed on a Mueller-Hinton agar plate inoculated with *E. coli* ATCC 25922. The test strain was then streaked radially from the edge of the disk to the periphery of the plate. After overnight incubation, the presence of distorted zone was observed.

Phenotypic confirmation tests

The Mastdiscs ID inhibitor combination disk method (Mast Diagnostics), Rosco Diagnostica Neo-Sensitabs (RDS), consists of 4 disks: disk A, containing a carbapenem (meropenem, 10 μg); disk B, consisting of meropenem (10 μg) and an MBL inhibitor; disk C, consisting of meropenem (10 μg) with a KPC inhibitor; and disk D, containing meropenem (10 μg) with an AmpC inhibitor. The interpretation of the test is as follows. The zone of inhibition of disk A is compared to the zones of inhibition of each of disks B, C, and D. If disk B shows a zone difference of ≥ 5 mm from disk A, the organism is recorded as demonstrating MBL activity. If disk C shows a zone difference of ≥ 4 mm from disk A, the organism is recorded as demonstrating KPC activity. If disk C and disk D shows a zone difference of ≥ 4 and ≥ 5 mm, respectively, from disk A, the organism is recorded as demonstrating AmpC activity coupled with porin loss (impermeability). Genotypic testing (ESBLs and Carbapenemases genes detection) were done with microarray analysis (CheckPoints BV, Wageningen, Netherlands) at the reference laboratory (Tables 1-3).

Organism	KLPN	E-test Result for the MIC of some antibiotics IMIPENEM 4 MEROPENEM 8 COLISTIN 0.38 TGC 1.5
Ad Date		
AK	S	
AMC	S	
AMP	R	
ATM	R	
CAZ	R	
CIP	R	
CRO	R	
CTX	R	
CXM	R	
FEP	R	
FOX	R	
GM	R	
IMP	R	
MEP	R	
PTZ	R	
SXT	R	

Table 1: Phenotypic testing.

Cartridge A-Carbapenem 10 microgram/mm	14
Cartridge B-Carbapenem 10 microgram+MBL inhibitor discs/mm	23
Cartridge C-Carbapenem 10 microgram+KPC inhibitor discs/mm	12
Cartridge D-Carbapenem 10 microgram+AmpC inhibitor discs/mm	15
Cartridge B-Cartridge A	9
Cartridge C-Cartridge A	-2
Cartridge D-Cartridge A	1
Interpretation	Positive for MBL

Table 2: Mast Disk Result.

Molecular Result	ESBL CARBA
KPC	NO
NDM 1	Yes

ESBL	Yes
All TEM, TEM_E104K, TEM_R164S,TEM_R164C,TEM_R164H,TEM_G238S	NO
All SHV	Yes

SHV_238G	Yes
SHV_G238S	NO
SHV_G238A	NO
SHV_240E	Yes
SHV_E240K	NO
CTX-M I	Yes
CTX-M 2	NO
CTXM-9	NO
CTXM 8-25	NO
CARBA	Yes
All VIM	NO
VIM I	NO
VIM II	NO
OXA 48	NO
IMP I	NO
IMP II	NO

Table 3: Molecular Result.

Discussion

New Delhi Metallo-B- Lactamase 1 (NDM-1) has been detected first in *Klebsiella pneumoniae* isolated from Swedish patients of Indian origin in 2008. It was detected at a later time in India, Pakistan, United Kingdom, United States, Canada, Japan and Brazil. The most common bacteria carrying them are Gram-negatives, such as *E. coli* and *Klebsiella pneumoniae*, but the genes for NDM-1 can be spread from one strain of bacteria to another through horizontal gene transfer [1].

In the early 1940s, even before the clinical use of penicillin, the β-Lactamases were described to be able to destroy penicillin. The development of compounds resistant to β-Lactamases (e.g. cephalosporins and carbapenems) or having the ability to inactivate them (e.g., β-Lactamase inhibitors) has simply been met with the evolution of new β-Lactamases, often through mutations that inactivate these antibiotics. At present, more than 890 such unique enzymes have been discovered; even more than the antibiotics developed against them [2,3].

K. pneumoniae containing NDM-1 was first discovered in 2008. By 2009, a study in Mumbai revealed 24 carbapenem-resistant Enterobacteriaceae, 22 of which were NDM-1 producers. Of these 22 organisms, 10 were *klebsiella* species, 9 were *Escherichia coli*, 2 were *enterobacter* species, and 1 was *Morganella morganii* — illustrating the ability of the plasmid to spread rapidly among strains of Enterobacteriaceae. Another recent study has shown distribution of NDM-1 producing Enterobacteriaceae affecting large area in Bangladesh, Pakistan, and UK, all of which appears to have happened since the original isolate was discovered in 2008 [1].

In Oman the first NDM-1 reported in the Middle East were obtained from a patient previously admitted to an Indian hospital for pneumonia in March 2009 who was transferred to Oman and admitted to the intensive care unit (ICU), a multidrug-resistant *K. pneumoniae* (designated strain 601) that was resistant to all b-lactams including carbapenems.

The case presented here had recurrent bouts of bacteremia due to biliary sepsis with ESBL *E. Coli* that was not properly treated for a long time; he then went to India, where he had biliary invasive procedures, possibly introducing a new set of bacteria carrying the NDM-1 mutation. He was subsequently treated for both ESBL and NDM-1 with two classes of antibiotics; he cleared the infection at the end. Tigecycline was not chosen due to its poor biliary bioavailability, and colistin was planned to be started as salvage therapy of if he did not respond to amikacin and imipenem [4,5]. Strict infection control measures were implemented to this case, which is a cornerstone in the management of these infections.

We believe that this is the first case of an NDM-1 carrying bacteria in Saudi Arabia, as there has been no reported cases at the time of this writing.

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