Case Report

Campylobacter jejuni ssp. jejuni bacteraemia in a patient with BCR-ABL-positive chronic myelogenous leukaemia in remission on dasatinib therapy

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Introduction: We report an unusual case of Campylobacter jejuni bacteraemia in a patient with Philadelphia chromosome-positive, BCR-ABL-positive chronic myelogenous leukaemia in complete cytogenetic and major molecular remission after dasatinib/IFN therapy.

Case presentation: On admission, the patient presented with fever and acute haemorrhagic diarrhoea. Initial empiric antibiotics consisted of ceftriaxone and metronidazole. Stool and blood culture samples were collected and submitted for evaluation; these specimens were processed as per laboratory protocol. Several Gram-negative, spiral rods could be identified microscopically in Gram-stained slides from bottled blood and stool cultures. Isolate identification was performed on the Vitek 2 system using a GN identification card and API Campy strips and by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS). Discrepant identification was obtained between the Vitek versus the API Campy test and MALDI-TOF. Erythromycin susceptibility testing was done using an Etest, whereas all other susceptibility testing and breakpoint analysis was done following the EUCAST procedure. Initial empiric antibiotic treatment was switched from ceftriaxone to ciprofloxacin according to antibiotic susceptibility testing (AST) and Etest (ciprofloxacin MIC of 0.094 µg ml⁻¹ results). C. jejuni bacteraemia was successfully eradicated after 1 week of ciprofloxacin therapy.

Conclusion: This case describes the rare event of a Campylobacter bacteraemia, which could have been falsely interpreted because of non-specific colony morphology and the initial Vitek result. Only the combination of microscopy, MALDI-TOF and an API Campy test was able to rapidly identify this bacterium as C. jejuni. This case also shows the importance of immediate AST- and MIC-adapted antibiotic treatment in immunocompromised febrile patients suffering from Campylobacter-induced bloody diarrhoea.

Keywords: bacteraemia; Campylobacter; MALDI-TOF.

Introduction
Campylobacter is a food-borne enteropathogenic bacterium that usually causes diarrhoea in healthy adults (Pacanowski et al., 2008; Ben-Shimol et al., 2013). In immunocompromised patients, Campylobacter-induced clinical symptoms can be much more severe (Ariganello et al., 2013; Brah et al., 2011; van der Bruele et al., 2010; Romero Gómez et al., 2010; Hopkins et al., 2011). Campylobacter spp. represent a growing clinical problem as they are widespread in the poultry industry and show increasing antibiotic resistance capabilities (Allos, 2001; Feodoroff et al., 2011; Shimizu et al., 2012).

Case report
We report on a 25-year-old male patient with acute-onset bloody diarrhoea, abdominal pain, headache, rheumatic pain, fever (39.9 °C) and generalized malaise. His medical history revealed Philadelphia chromosome- and...
BCR-ABL-positive chronic phase, low-risk (EUTOS score) chronic myelogenous leukaemia (CML). The patient had achieved complete cytogenetic remission after 3 months of treatment with the oral tyrosine kinase inhibitor nilotinib (Tasigna®, Novartis, Basel, Switzerland). He was on a reduced dose of nilotinib (450 mg day⁻¹) due to a mild form of liver toxicity, and was switched to dasatinib (Sprycel®, Bristol Myers Squibb, Princeton, USA) a few months after initial diagnosis. After switching to dasatinib plus IFN, the patient suffered from nausea and bloody vomiting. Gastroscopy from that time showed a mild form of gastritis and thus pantoprazol was administered. On clinical examination, patient had epigastric pain and bloody stools. His calcium normal ranges: i) calcium 2.2 – 2.65 mmol l⁻¹; ii) hemoglobin: 7.6 – 9.5 mmol l⁻¹; iii) platelet count: 150 – 360 × 10⁹ l⁻¹; iv) CRP: <7.5 mg l⁻¹ (2.12 mmol l⁻¹), haemoglobin (7.7 mmol l⁻¹) and platelet count (112 × 10⁹ l⁻¹) were low. His C-reactive protein (146.9 mg l⁻¹) was highly elevated. The peripheral blood leukocyte count (4.6 × 10⁹ l⁻¹), absolute number of granulocytes (2.48 × 10⁹ l⁻¹) and percentage of segmented granulocytes (52 %) were within the normal range. The percentage of neutrophilic granulocyte precursor cells was elevated (8 %), and atypical lymphocytes (2 %) were detected in the peripheral blood. At the time of hospitalization, the patient was immediately rehydrated and empiric antibiotic treatment with ceftriaxone and metronidazole was started. Under this treatment, his inflammation markers were declining, his clinical symptoms improved and the bloody diarrhoea episodes halted.

Investigations

Specimens were obtained from the patient’s stool and blood for microbiological analysis. Stool samples were routinely streaked on Salmonella-Shigella, Hektoen and Yersinia agar. Selective Campylobacter agar (Butzler et al., 1973) containing five antimicrobials (novobiocin, bacitracin, colistin, cephalzin, cycloheximide) was used for the enrichment of Campylobacter spp. For API identification, organisms were grown on Columbia agar plates under microaerophilic conditions (42 °C, 24 h). Blood cultures were incubated using a BacT/ALERT (bioMérieux) blood culture system. Staining was done by Gram staining and Gram’s safranin solution (Merck-Millipore KgaA). Microscopic analysis was performed using an Axio microscope, and slide pictures were taken with an attached AxioCam MR camera (Zeiss). The isolate was identified by an API Campy and Vitek 2 system using a GN identification card (both from bioMérieux). Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS; bioMérieux and Shimadzu) was conducted in order to cross-check previous results obtained using the Vitek system. Antibiotic susceptibility testing (AST) was performed using agar diffusion. The MIC for erythromycin was determined with an Etest (Liofilchem).

Results

We report on a 25 years-old male patient with an acute onset of acute bloody diarrhoea, abdominal pain, headache, rheumatic pain, fever (39.9°C) and generalized malaise. His medical history revealed a Philadelphia-chromosome- and BCR-ABL-positive chronic phase, low-risk (EUTOS score) chronic myelogenous leukaemia (CML). Patient achieved complete cytogenetic remission after 3 months of treatment with the oral tyrosine kinase inhibitor nilotinib. He was on reduced dose of nilotinib (450mg/d) due to a mild form of liver toxicity, and was switched to dasatinib a few months after initial diagnosis. After switching to dasatinib plus interferon, patient suffered from nausea and imbrued vomiting. Gastroscopy from that time showed a mild form of gastritis, thus pantoprazol was administered. On clinical examination, patient had epigastric pain and bloody stool. Calcium (2.12 mmol/l), hemoglobin (7.7 mmol/l), and platelet count (112 Gpt/l) were low. C-reactive protein (CRP) (146.9 mg/l) was highly elevated. Peripheral blood leukocyte count (4.6 Gpt/l), absolute number of granulocytes (2.48 Gpt/l) and percentage of segmented granulocytes (52%) were in normal range. Percentage of neutrophiic granulocyte precursor cells was elevated (8%), and atypical lymphocytes (2%) were detected in peripheral blood. At time of hospitalisation,
patient was immediately rehydrated and empiric antibiotic treatment with ceftriaxone and metronidazole was started. Under this treatment inflammation markers were declining, clinical symptoms improved and bloody diarrhoea episodes halted.

Stool culture signals were positive using biochemical tests for *Campylobacter jejuni*. Blood cultures were indicated as positive after incubation, and aliquots from bottled blood cultures were Gram stained. Several Gram-negative rods could be identified under magnification (Fig. 1). Staining with Gram’s safranin solution lead to an improved visibility of Gram-negative, spiral rods, with a length of 2–5 μm (Fig. 2). After 2 days of incubation, confluent, grey, non-haemolytic colonies were visible on *Campylobacter* agar for which oxidase and catalase testing was positive. MALDI-TOF MS was carried out to assist in diagnosis and also revealed *C. jejuni*. Biochemical tests for cytochrome c oxidase and catalase were positive. Additional biochemical analysis was performed using an API Campy test, in accordance with the manufacturer’s instructions. Species identification was confirmed by API Campy biochemical testing with a 99.9 % probability for *C. jejuni* ssp. *jejuni*. Conventional agar diffusion AST showed resistance to cephalosporins and ampicillin. Etests for erythromycin (MIC 0.25 μg ml⁻¹), ciprofloxacin (MIC 0.094 μg ml⁻¹) and doxycycline (MIC 0.125 μg ml⁻¹) (Fig. 3) showed no resistance to these drugs, according to EUCAST *Campylobacter* clinical breakpoints.

**Outcome**

Antibiotic treatment was switched from initial empiric ceftriaxone to ciprofloxacin, according to the AST results. The patient was dismissed home after successful treatment with ciprofloxacin (500 mg day⁻¹) for 7 days.

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**Fig. 2.** *Campylobacter* (Gram-negative- spiral rods) in stool culture (left panel) and blood culture (right panel). Magnification × 1000; enlargements are shown in the insets. Gram’s safranin solution staining, under dark light, using a Zeiss Axio microscope (Zeiss).

**Fig. 3.** Determination of MICs using Etests (Liofilchem) for ciprofloxacin (left), doxycycline (centre) and erythromycin (right).
Discussion

The reasons why some C. jejuni isolates cause sepsis are not yet fully understood, but underlying malignant haematological disease is certainly one major reason for their ability to invade the bloodstream (Aggarwal et al., 2010; Nielsen et al., 2010; Shiferson et al., 2009; Wong et al., 2009; Fernández-Cruz et al., 2010; Gazeigne et al., 2008). The CML-directed second-generation BCR-ABL tyrosine kinase inhibitor dasatinib has a well-known side effect profile with reported grade 3–4 cytopenias (10–21 %) in previous phase III studies (Kantarjian et al., 2010; Hochhaus & Kantarjian, 2013; Lindauer & Hochhaus, 2014). In addition to the BCR-ABL target oncogene, dasatinib inhibits additional kinases, such as SRC and c-KIT. This inhibition might have an impact on adequate immune system responses following dasatinib treatment. Dasatinib may enhance or suppress T-cells (Nerreter et al., 2013). Although our patient did not suffer from leukopenia at the time of Campylobacter-induced sepsis, further antibiotic treatment against C. jejuni was medically indicated due to the patient’s underlying disease and invasive gastrointestinal infection (Allos et al., 2001; Ledina et al., 2012). This case demonstrates the importance of rapid identification of bacterial isolates from positive blood cultures by MALDI-TOF MS (Martiny et al., 2011). This allows the immediate AST–MIC-adapted EUCAST-recommended antibiotic treatment in immunocompromised febrile patients suffering from Campylobacter-induced haemorrhagic diarrhoea. It remains unclear whether this reported Campylobacter sepsis case was related to previous dasatinib therapy, underlying CML disease or a highly virulent Campylobacter strain (Wu et al., 2013; Lemaire et al., 2010). Further clinical studies are warranted in this respect.

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References


