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Case Report

A Young Child with Locally Acquired Refractory Brucellosis

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Abstract Brucellosis, although not prevalent in Hong Kong, is a challenging zoonotic disease in terms of management and diagnosis. It is often overlooked and misdiagnosed in areas of low prevalence, and treatment strategy is different in paediatric population due to the limitation in drug choices and potential medication side effects. We report a 30-month-old boy with refractory brucellosis who presented with pyrexia of unknown origin.

Key words *Brucella melitensis*; Brucellosis; Pyrexia of unknown origin

Case Report

A 30-month-old locally-born Chinese boy was first referred to our university-affiliated teaching hospital with an 8-day history of high fever without any obvious focus in April 2017. His family admitted that this child fed goat and contacted goat's face in Sai Kung earlier that month. However, he had not been bitten by goats or consumed any unpasteurised milk or undercooked meat. He did not travel outside of Hong Kong in the past 6 months, and his close contacts had been well. His younger brother also fed goat on the same occasion but remained well. Child enjoyed good past health with no history of recurrent infections. His parents were non-consanguineous, and family history was unremarkable.

Patient already had fever for 4 days upon admission to a private hospital, and was empirically covered with IV Cefotaxime and oral Zithromax during his stay. Child was then referred to our unit for further care. Fever was gradually settling, but blood culture taken at private, yielded gram-negative bacilli after incubation for 8 days, and only came back positive for *Brucella species* on the 10th day of culture. After identification of *Brucella species*, child was immediately put back on a combination of **intravenous gentamicin 60 mg Q24H (BW 12.3 kg, 5 mg/kg/dose) and oral co-trimoxazole 360 mg BD (Trimethoprim 10 mg/kg/day and sulfamethoxazole 50 mg/kg/day) for 10 days** followed by **oral co-trimoxazole 360 mg BD and rifampicin 100 mg BD (~16 mg/kg/day) for 5 more weeks**. Report on the antibiotic sensitivity was delayed till the 15th day of culture, showing susceptibility to trimethoprim/sulfamethoxazole (MIC: 0.25/4.75 mcg/ml) and gentamicin (MIC: 0.5 mg/ml). Gentamicin level was sufficient (pre-dose <0.3; post-dose 10.03), and drug compliance was reported to be satisfactory. Blood culture repeated five days after commencement of antibiotics came back negative. Skeletal survey found no bony lesions. Clinically, his fever subsided and clinical condition improved.

Child presented again with fever for three days, vomiting and 'tired' feeling of his neck on the first week of September 2017. This was around 15 weeks after discontinuation of all antibiotics. Upon admission to a private hospital, he was found to have skin mottling on examination. His complete blood count, C-reactive protein and erythrocyte sedimentation rate were normal, but his liver transaminases

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were raised (ALT 185 IU/L, AST 148 IU/L). Virological workup was negative. Child was empirically covered with intravenous cefotaxime for 4 days, then changed to intravenous meropenem and amikacin in view of persistent fever. Blood culture revealed gram negative bacilli five days after admission, and later identified *Brucella melitensis*.

Child was then transferred to our hospital for further management on day 8 of illness. He had high swinging fever and tachycardia with pulse rate of 140/min despite almost 3 days of intravenous meropenem and amikacin. He was started back on **oral co-trimoxazole 360 mg BD and rifampicin 140 mg BD (BW 14 kg, 20 mg/kg/day)**, but later changed to **intravenous gentamicin 100 mg Q24H (7 mg/kg/dose) in addition to oral co-trimoxazole 360 mg BD** in view of deranged liver enzymes (ALT 396 IU/L) and thrombocytopaenia (Figure 1). Hepatitis workup excluded hepatitis B, hepatitis C, cytomegalovirus and Epstein-Barr virus infections. Ultrasound abdomen was unremarkable and cerebrospinal fluid examination was also normal.

Blood culture on admission to our ward was also positive for *Brucella melitensis* after 5 days of incubation (Figure 2), and showed in-vitro sensitivity to co-trimoxazole (Minimal inhibitory concentration [MIC] 0.06 mg/mL), gentamicin (MIC 2.0 mg/mL), tetracycline (0.25 mg/mL) and ciprofloxacin (MIC 1.0 mg/mL). Bone marrow aspirate also isolated *Brucella melitensis*, so did repeated blood cultures taken 7 and 11 days later. Gentamicin peak levels were aimed at higher values this time (16-24 ug/ml) but remained suboptimal (pre-dose <0.3-0.68; post-dose 5.3-8.44) despite repeated increment in dosage. Antibiotics were stepped up in view of persistently positive blood cultures. Following the recovery of platelet count and deranged liver enzymes, **oral rifampicin 110 mg BD (15 mg/kg/day) and intravenous ciprofloxacin 140 mg Q8H (10 mg/kg/dose)** were added on days 12 and 19 respectively, while gentamicin was discontinued after 14 days. Bone scan did not show any suspicious osseous activities or occult infection, but PET scan showed a non-specific hypermetabolic focus (SUVmax 2.1) over the right sided mid-abdomen likely in the small bowel, which has higher uptake than physiological bowel activity. Patient, however, did not exhibit symptoms of gastro-intestinal disturbances. Blood culture taken on day 19 was finally negative, which remained sterile after extended incubation for 21 days.

During the antibiotic course, patient's neutrophil count dropped to a nadir of 0.5×10^9/L, which was likely to be attributed to the side effects of septrin. Neutrophil count was closely monitored, and it returned to the normal range after a week. In addition, patient developed maculopapular

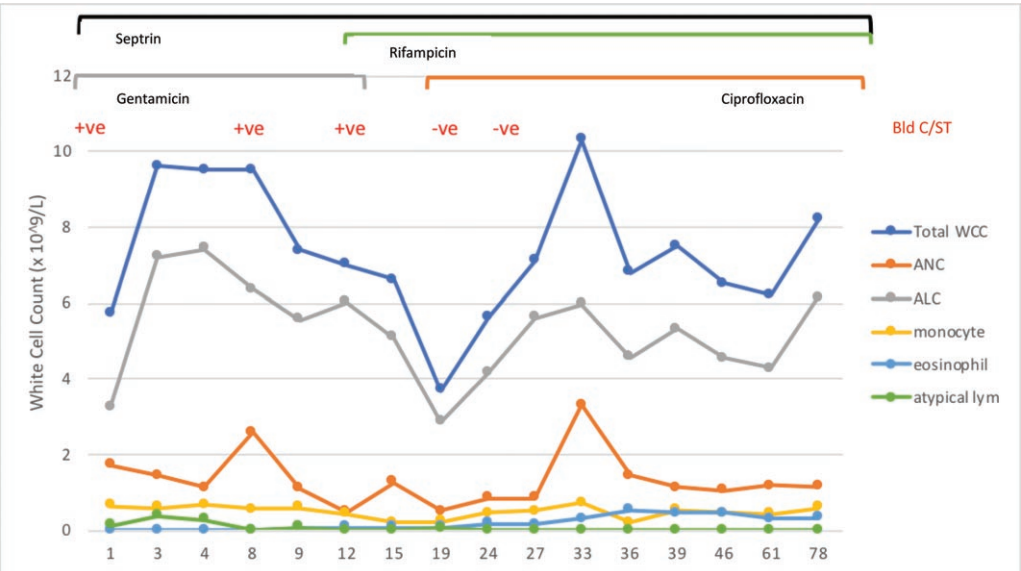

Figure 1 Time trend of total & differential counts of peripheral blood leukocytes & blood culture positivity in accordance with antibiotic treatment.

rash around four days after the addition of rifampicin and before ciprofloxacin. Serum creatinine concentration also increased on week 4 of treatment to 133 mmol/L (GFR 26 ml/min/1.73m^2). These features suggested possible delayed hypersensitivity reaction to rifampicin. However, taken into account the mild severity of drug rash and spontaneous resolution of his renal impairment after a week, child was continued on triple therapy with **oral co-trimoxazole, rifampicin and ciprofloxacin.** Follow-up whole-body CT scan after 2 months showed resolution of previous increased SUV activity at small bowel, and specifically there were no evidence of sacroiliitis and spondylodiskitis. Ciprofloxacin was off after a 4-week course, with continuation of oral rifampicin and co-trimoxazole for a total duration of 4 months after the last positive blood culture. Further follow-up 6 weeks after cessation of antibiotics has been arranged.

Discussion

B. melitensis is the most virulent among all *Brucella species*, which causes a severely debilitating and disabling illness. Brucellosis is transmitted from animals to humans by consumption of unpasteurised dairy products, consumption of undercooked meat, or skin penetration after contact with infected animals.[1] Our patient was likely to acquire brucellosis after direct contact with goat's mucosa. Interestingly, his family members who have goat contact on the same occasion remained asymptomatic.

Symptoms of brucellosis may occur anytime from five days to five months after initial exposure to *Brucella species*, and should be considered as a differential diagnosis for fever of unknown origin. In situations where complications are not promptly recognised and treated, death occurs in 2% of cases of which endocarditis is the commonest cause. In addition, a high index of suspicion is required to maximise the recovery of the organism by prolonged incubation. Physicians should also be cautious about the lower blood culture yield with prior antibiotic treatment.[2]

Due to high relapse rate of 10-20% in patients receiving monotherapy, brucellosis should be treated with an aminoglycoside in addition to tetracyclines for 6 weeks in adults.[3-8] Tetracyclines are avoided in children under eight years old because of the potential for permanent staining of deciduous teeth and inhibition of bone growth. Hence, these young children could receive co-trimoxazole, rifampicin and ciprofloxacin alternatively. The use of ciprofloxacin has been limited by the potential arthropathy in young children. Cartilage and tendon damage was noticed in weight bearing joints of juvenile animals, and arthralgia is not uncommonly reported as an adverse effect after use of ciprofloxacin in children.[9] Previous systematic reviews have shown that co-trimoxazole and rifampicin-based therapies were associated with higher rate of brucellosis relapse. This combination of co-trimoxazole and rifampicin gave undesirable result (p=0.646 for relapse,

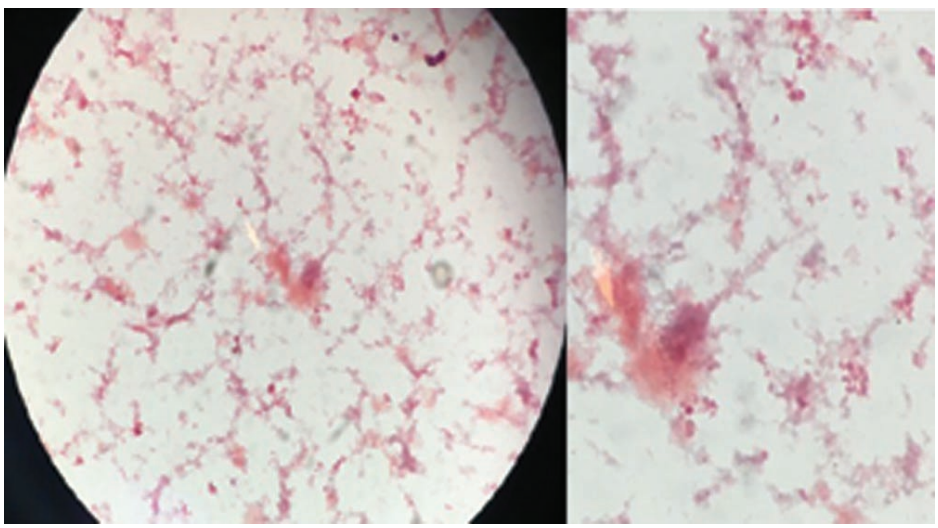

Figure 2 Photomicrograph of *Brucella melitensis* showing small, gram-negative, non-motile, non-spore-forming and rod-shaped (coccobacilli) bacteria.

p=0.02 for treatment failure, and p=0.028 for the combined variable of relapse and treatment failure). This might be overcome by extended treatment duration to at least 8 weeks, or if co-trimoxazole was combined with doxycycline.[6,7] This is supported by another recently published Iranian study in which clinical isolates of *Brucella melitensis* have decreased sensitivity to rifampicin in 35.1% of isolates, and less in co-trimoxazole (3.5%) as compared to 5 other antibiotics.[10]

Conclusion

Physicians should be aware that brucellosis can be acquired locally. This case highlighted the difficulty in treating brucellosis in children. Prolonged course of dual or even triple antibiotics are important treatment strategy for brucellosis in children, although physicians should closely monitor the side effects of such treatment. One of the reasons leading to brucellosis relapse in our patient might be due to the reduced susceptibility to rifampicin in addition to inadequate treatment duration in this regard. The persistently positive cultures after initial treatment of relapsed brucellosis was possibly due to the inability to achieve optimal gentamicin peak levels relative to the MIC of *B. melitensis* to gentamicin (ideally 10:1). It is useful to add a third antibiotic earlier on, to test the sensitivity profile and MIC of *B. melitensis* to rifampicin, and to prolong the antibiotic course to at least 3 months.

Conflict of Interest

We declare that we have no conflict of interest.

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