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QUEST FOR THE DIAGNOSIS

Case 1: A neonatal zoonosis

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CASE

A 20-year-old primigravida, who was in the 39th week of gestation, was admitted to the maternity ward in labour. She had been well throughout pregnancy and her antenatal foetal ultrasound scans had shown a normal developing foetus. The amniotic membranes ruptured spontaneously and the liquor was clear. However 15 h following membrane rupture she was still in the first stage of labour. She had developed a fever of 38°C and the liquor was noted to have become foul smelling. The cardiotocogram did not reveal any signs of foetal distress. In view of evidence of chorioamnionitis she was started on intravenous co-amoxiclav, and was taken urgently to the operating theatre where a female neonate was delivered by an emergency Caesarean section.

At birth the newborn was floppy and pale, and needed bag and mask ventilation with oxygen for a few minutes due to a poor respiratory effort. Apgar scores were 7, 8 and 9 at 1, 5 and 10 min, respectively. Following resuscitation she was noted to be tachypnoeic and hypotonic, and was transferred to intensive care. She weighed 3.56 kg (P50th) and her occipitofrontal circumference measured 36 cm (P90th). Her core temperature was 37.5°C. Blood investigations, including blood cultures, were taken from a peripheral vein at 1 h of age; however, no antibiotics were initiated. Her full blood count showed a total white cell count of 35.6×10^9/l, a neutrophil count of 23×10^9/l, a haemoglobin concentration of 12.3 g/dl with a haematocrit of 36.2% and a platelet count of 301×10^9/l. Her acid base balance and renal function were within normal limits. She required oxygen supplementation via nasal prongs and was given nasogastric feeds. Due to recurrent vomiting and irritability on handling, a chest X-ray and lumbar puncture were performed at 18 h of age. Blood-stained cerebrospinal fluid (CSF) was obtained from the traumatic spinal tap. Biochemical and cytological analyses could not be performed on the small volume of CSF; however, there was sufficient amount that could be sent for culture. Following the lumbar puncture she was started on intravenous co-amoxiclav (30 mg/kg twice daily) and cefotaxime (50 mg/kg twice daily), according to the unit's standard protocol for treatment of ill newborns with a history of chorioamnionitis at birth, and was supported with intravenous fluids. Her chest X-ray showed clear lung fields with a small right basal pneumothorax, which was treated conservatively. She did not sustain a rise in her C-reactive protein taken at 1 h of age and 24 h later. No organisms were cultured from the CSF. However, on the fifth day Gram-negative coccobacilli were isolated from her blood cultures. At this time she was off oxygen and feeding orally, with no further signs of sepsis or cardiorespiratory compromise.

Identification of the microorganism isolated from this neonate's blood was surprising as it is usually found as an oral commensal in cats and dogs. A careful reassessment of the maternal history revealed that two weeks prior to the delivery she had taken care of a puppy for a couple of days. She was not bitten by the dog but was licked several times on the hands. What is the diagnosis?

Case 2: Abdominal discomfort and generalized oedema in a 6-year-old boy

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CASE

A previously healthy 6-year-old boy from the rural zone presented with a 20-day history of vomiting, salivation and asthenia, associated with epigastric pain and lower limbs oedema for the last 8 days. He had facial, tongue and lower limb oedema; in addition to a palpable gastric border, auscultation revealed decreased breath sound. He refused food. The laboratory evaluation showed polycithemia (red blood cells/mm^3 5 300 000, Hb 15.3 g/dL, Ht 43.9%), eosinophilia (white blood cells/mm^3 14 300, 13% eosinophils), hypoalbuminemia (1.4 g/dL) and prolonged prothrombin time (38.6 sec). Hepatic enzymes, creatinine and blood urea nitrogen were normal and there was no proteinuria in the 24-h urine examination. Cytomegalovirus (CMV)-specific IgG and IgM were positive and negative, respectively, and negative serology tests to Hepatitis A, B and C were found. Three consecutive samples of faeces showed no parasite. Chest X-ray showed bilateral pleural effusion. Abdominal ultrasonography found a small amount of ascitic fluid and diffuse thickening of the gastric mucosa. Computerized tomography study showed giant gastric folds without enlarged lymph nodes or tumour. At admission, daily ranitidine (4 mg/kg twice a day) was started and he received intravenous albumin (one infusion) and vitamin K (for 3 days) with resolution of the oedema and prothrombin time normalization but persistent abdominal discomfort. At the 14th day of hospitalization, upper gastrointestinal endoscopy found hypertrophic gastric rugae, oedematous and fragile mucosa of the gastric fundus and body, with nodules and plain ulcers recovered by fibrin; the antrum mucosa was unremarkable. Omeprazole (1.5 mg/kg/day) was initiated and complete resolution of the complaints occurred on the fourth day of use. He was discharged at the 30th day of hospitalization and his first reevaluation at the outpatient setting was 25 days after discharge. He received omeprazole for 14 days. Any complaint was denied and physical findings were not found after the resolution of the symptoms at every reevaluation. His last follow-up examination occurred 7 months after discharge.

DISCUSSION

Case 1

The case we describe is an example of an unusual neonatal zoonosis caused by *Pasteurella multocida*, which was responsible for the signs of septicaemia in this neonate. Zoonotic infections in newborns, such as toxoplasmosis, listeriosis and brucellosis, occur as a result of transmission of microorganisms from infected animals to the gravid mother, and subsequently to her infant. Another serious but rare neonatal zoonosis may be caused by *Pasteurella multocida*, a Gram-negative coccobacillus that is a pathogen in a wide range of animal species, including fowl, rabbits and cattle, and a common commensal in the upper respiratory tract of domestic cats and dogs (1,2). Neonatal infections secondary to *P. multocida* can be acquired vertically from maternal exposure (3–5) or postnatally from animal contact (6). The global incidence and prevalence rates of *P. multocida* infections are unknown because, as yet, it is not a notifiable disease in several countries. However, *P. multocida* has been identified as the aetiological agent of several infectious disease presentations (7). Data taken from published case reports and literature reviews indicate that the risk of human transmission is rare despite the popularity of domestic cats and dogs (4,7).

Human infections caused by *P. multocida* are classified under three categories: local, pulmonary and opportunistic. Direct inoculation of the organism from animal scratches, bites or even licks may result in wound cellulitis and lymphadenitis but can, at times, become complicated with abscess formation, tenosynovitis, septic arthritis or osteomyelitis especially if the fingers or hands are bitten (7). The respiratory tract of patients with underlying pulmonary disorders may become colonized with *P. multocida*, frequently without any untoward effect; however, pneumonia, empyema and lung abscesses may develop if the organism invades lung tissue (7). Serious opportunistic infections consisting of bacteraemia in patients with liver disease, septic arthritis in diseased joints, and central nervous system infections and meningitis in the elderly and the very young, especially neonates, have also been reported (2–4,7,8). The relatively immature immune system of neonates and infants increases their risk for invasive infections such as septicaemia, meningitis and osteomyelitis (2–10). Furthermore, the ability of *P. multocida* to colonize the female genital tract during pregnancy has not only been associated with secondary chorioamnionitis and invasive infections of the newborn (3,5) but also with puerperal sepsis (11).

The short incubation period of *P. multocida*, which is less than 24 h, is consistent with the early appearance of this neonate's bacteraemia and clinical picture. Although we do not have any cultures of the maternal blood, amniotic fluid or the vaginal tract to prove vertical transmission, we speculate that the most likely source of infection was the maternal genital tract. Subsequent ascending infection following rupture of the amniotic membranes could have led to chorioamnionitis and neonatal septicaemia. Inoculation of the maternal genital tract might have occurred during pregnancy following contact with the puppy's saliva and subsequent inappropriate hand hygiene prior to toileting.

The Gram-negative coccobacilli isolated from the blood cultures of the neonate we describe were identified as *P. multocida* with a panel of biochemical tests using ID32E (bioMérieux, Marcy-l' Etoile, France). The isolated *P. multocida* strain was sensitive to ampicillin, co-trimoxazole, co-amoxiclav, gentamicin, ciprofloxacin and imipenem with intermediate resistance to ceftazidime. The initial choice of co-amoxiclav and cefotaxime was not altered in view of the subsequent good clinical response, and treatment was continued for a total of 10 days. However, the intravenous administration of a narrower spectrum antibiotic such as high-dose penicillin, which is the recommended treatment for *P. multocida* infection, would have also been suitable. Blood cultures were not repeated during treatment because

there were no further signs of sepsis after initiation of antibiotics. Following discontinuation of the antimicrobials, the neonate was observed in hospital for a further 24 h, and because she remained well, with no signs of sepsis, no control blood cultures were taken. No complications were subsequently identified and her development at 18 months was normal.

Despite the reported high mortality following neonatal *P. multocida* infections (4), we believe that the good outcome in our case was due to the lack of multiorgan failure and the administration of antibiotics, which co-incidentally were active against *Pasteurella*. Most neonatal antibiotic regimens used to treat early onset sepsis would have also been appropriate because these usually include benzylpenicillin or ampicillin, both of which are active against *Listeria monocytogenes*, an organism that causes neonatal zoonosis more frequently than *P. multocida*.

In conclusion, vertically transmitted *P. multocida* infections in neonates occur as a direct consequence of maternal exposure to cats or dogs, and as we speculate in the case we have described, it can occur even after nontraumatic contact such as licking. The importance of hygienic precautions needs to be emphasized not only during pregnancy but also during routine infant care in order to avoid potentially devastating infections secondary to *P. multocida*. Furthermore, neonatal contact with animals should be discouraged.

DIAGNOSIS

Neonatal *Pasteurella multocida* septicaemia

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DISCUSSION

Case 2

Biopsy of the gastric body performed during the upper gastrointestinal endoscopy revealed foveolar hyperplasia with cystic dilatation of the glands and Ménétrier disease (MD) was diagnosed (Fig. 1). No sign of *Helicobacter pylori* by the Giemsa method, of CMV inclusion body or of malignancy was found.

MD (hypertrophic protein-losing gastropathy) is a rare illness; since its first description in 1888, around 360 cases have been reported (1), out of which around 60 were among children (2). The aetiology is unknown but gastric CMV infection and transforming growth factor-alpha overexpression have been implicated in the pathogenesis (3). Clinical findings among children include oedema, ascites, pleural effusion due to hypoalbuminemia in the absence of malnutrition, renal, hepatic or cardiac disease. Therefore, MD is a diagnosis to be investigated when a patient presents with generalized oedema (1).

Image examinations (abdominal radiograph, ultrasonography, computerized tomography study) show the characteristic hypertrophic gastric folds (4). The upper gastrointestinal endoscopy is useful in confirming the diagnosis of MD by direct observation and in obtaining biopsy material to accurately establish this diagnosis and exclude other conditions which may mimic this disorder (3). The histologic features are similar among adults and children and include foveolar hyperplasia of the gastric mucosa accompanied by mucus hypersecretion and glandular atrophy of the gastric body (2). CMV infection may be detected by the presence of CMV inclusion bodies in the biopsy or by CMV growth from gastric tissue (1). CMV infection has been detected in one third of MD cases among children (1,3). In our case, the child presented with typical complaints and image examination findings and the MD diagnosis was established by the endoscopy and the biopsy. Ongoing CMV infection could not be accurately established because the virus was not cultured.

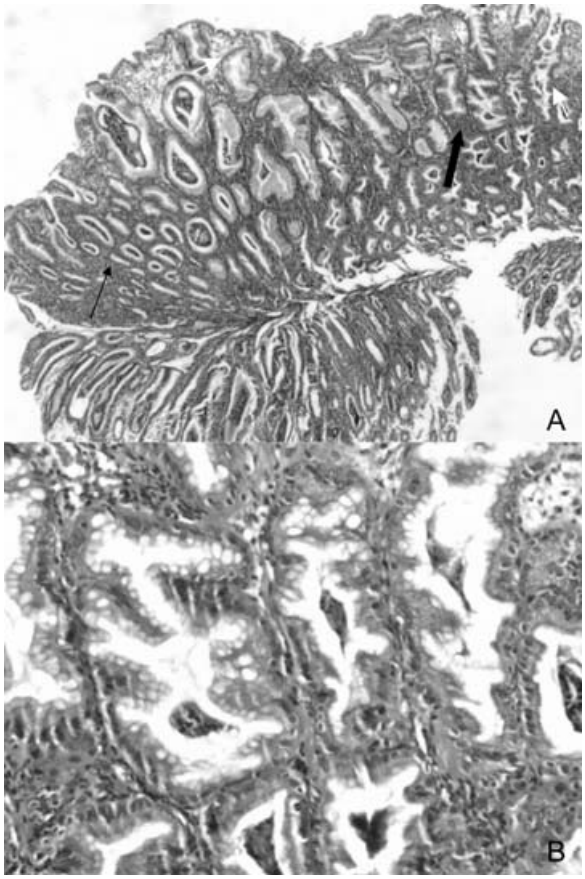

Figure 1 Microscopic section of the gastric mucosa of a boy with Ménétrier disease. Section A (×20): transition zone between normal (thin arrow) and hyperplastic (thick arrow) gastric glands. Section B (×100): detail of enlarged, tortuous and hyperplastic gastric glands (haematoxylin and eosin).

There is no consensus with regard to MD treatment and the use of antacids, H2-receptor antagonists, mucosa-protectives, octreotide, omeprazole or monoclonal antibody against the epidermal growth factor receptor and *H. pylori* eradication have improved the symptoms (5). Supportive treatment with a high-protein-diet and intravenous albumin transfusion may be helpful (6).

The gastritis due to *H. pylori* may mimic MD, clinically, endoscopically and histologically (7). The healing of H2-antagonist-resistant MD by eradication of *H. pylori* has been reported (8). A possible link between excess systemic endogenous production of glucagons-like peptide-2, a gut hormone that induces mucosal growth, and the hypertrophic gastropathy in a MD patient with *H. pylori* infection has been demonstrated (9). This is a possible physiopathogenic mechanism of the influence of *H. pylori* infection on occurrence of MD. In an experimental study, Mongolian gerbils infected with *H. pylori* and with gastric ulcers were treated by combined omeprazole and clarithromycin, as well as by each drug separately; the study showed that these drugs, in combination or separately, markedly enhanced ulcer healing and healed ulcers do not relapse, despite cessation of the drug treatment (8). Three MD adult cases unresponsive to H2-antagonists and without diagnosed infection showed marked response to omeprazole only (10,11). The temporal evolution of our case is suggestive of a MD child case unresponsive to H2-antagonist with clinical remission with omeprazole. We question if the long-term remission achieved could be due to *H. pylori* suppression and glucagons-like peptide-2 reduction that we were unable to document. To the best of our knowledge, this is the first case of a child with MD unsuccessfully treated with ranitidine who recovered fully following the use of omeprazole. We speculate that some additional omeprazole-related properties, like the antiapoptotic activity (12), could explain this finding.

Although paediatric MD is considered a transient condition, Konstantinidou et al. (2) reported that out of six patients with MD under 2 months of age, three received prostaglandin, five presented congenital defects and five died, suggesting that early infant MD might represent a separate subtype of the disease differing from the more common paediatric MD. Those authors proposed that MD should not be considered a specific disease but rather a reaction of the gastric mucosa to various insults, and the distinct manifestations of MD in the adult, paediatric and neonatal age groups represent an age-related phenotype (2).

MD appears to follow a characteristically benign course in children beyond 2 months of age, resolving within weeks to months, several of them with ongoing CMV infection (1). Because of MD rarity, no trials of medical treatment have been performed (10). For refractory or severe cases, we suggest the investigation of *H. pylori* infection and the use of omeprazole.

DIAGNOSIS

Ranitidine-resistant Ménétrier disease.

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