Necrotizing fasciitis caused by *Serratia marcescens* after tooth extraction in a Doberman Pinscher: a case report

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ABSTRACT: A 3-year-old Doberman Pinscher was referred to the Clinic for Small Animal Medicine and Surgery, Veterinary Faculty of Ljubljana for cardiologic examination due to lethargy, inappetence and lateral abdominal wall oedema. The dog had been treated at the primary veterinary practice for tooth granuloma two days before the presentation. During the course of the disease a presumptive diagnosis necrotizing fasciitis was ascertained and *Serratia marcescens* organism was isolated from the ventral body wall tissue, from the wound in the oral cavity and other organs in the body. Systemic signs developed concomitantly with the progression of the local disease. Due to grave prognosis the dog was euthanised. This is the first report of a necrotizing fasciitis in a dog caused by *S. marcescens* and also the first one suspected to occur after the dental procedure.

Keywords: fascial tissue infection; *Serratia marcescens*; dental procedure; dog

Necrotizing fasciitis (NF) is a rapidly progressive and potentially life-threatening bacterial infection of the subcutaneous and fascial tissues. A minor skin injury is the usual portal of entry, signs of infection appearing a few days later (Naidoo et al., 2005). In man NF has occurred following injections (Rieger et al., 2007), trauma (Liu et al., 2005), surgery (Piper and West, 1995) and pyelonephritis (Paya et al., 1998).

Infection causing bacteria produce the exotoxins (Carbonell et al., 2004) and proteinases (Akaike et al., 1989), and consecutively cause local thrombosis and tissue destruction. Poorly perfused and necrotic tissue allows further bacterial proliferation and invasion, spreading disease horizontally in the subcutaneous tissue and along affected fasciae.

The diagnosis is based on the clinical signs, which include localised erythema, oedema and pain of the affected area (Naidoo et al., 2005), surgical findings, histopathology results and positive culture of a recognised etiological agent (Liu et al., 2005).

Group A *Streptococcus* is the primary causative agent of NF in man (Cunningham et al., 2001), but other pathogens, particularly Enterobacteriaceae such as *Klebsiella pneumoniae, Aeromonas* spp., *Vibrio vulnificus* and *Pseudomonas aeruginosa* have also been reported as monomicrobial causes of NF. Polymicrobial synergistic infection is identified in up to 54% of patients, with streptococci and enterobacteriaceae being most common co-isolates (Wong et al., 2003). Only a few reports of NF exist in the veterinary literature (Prescott et al., 1997; DeWinter et al., 1999; Naidoo et al., 2005; Worth et al., 2005), mostly caused by *Streptococcus canis* (Prescott et al., 1997; DeWinter et al., 1999), with one report of NF associated with *Escherichia coli* (Worth et al., 2005). Concurrent signs of systemic illness, shock and multiorgan failure are well recognised in severe streptococcal infections, and streptococcal toxic shock syndrome (STSS) sometimes accompanies streptococcal NF (Naidoo et al., 2005).

S. marcescens is widely distributed in nature (Yang et al., 2007) and known to be an occasional cause of infection in man (Byrne et al., 2000; Bizzarro et al., 2007; Yang et al., 2007). It has been recognised to cause NF in immunocompromised people (Huang et al., 1999; Liangpunsakul and Pursell, 2001; Curtis et al., 2005), but it does not appear to have been

reported previously causing NF in dogs. Hereby, we report a case of NF caused by *S. marcescens* infection after the dental procedure and perioperative subcutaneous administration of amoxicillin-clavulanic acid suspension in a dog and illustrate some of the pitfalls in diagnosis and treatment of the condition.

Case presentation

A three-year old intact male Doberman Pinscher weighing 42 kg, was referred to the Clinic for Small Animal Medicine and Surgery at the Veterinary Faculty, University of Ljubljana for cardiologic examination. The referring veterinarian diagnosed heart failure and gave furosemide 2 mg/kg intravenously (*i.v.*) because of tachycardia, lateral abdominal wall swelling, lethargy and refusal of food two days after extraction of the maxillary right fourth premolar tooth, which had a periapical lesion. The dog had been treated with spiramycin and metronidazole (Stomorgyl 20) two tablets orally (*p.o.*) once daily for five days prior to the extraction, a single dose of amoxicillin-clavulanic acid 4.8 ml subcutaneously (*s.c.*) being administered perioperatively.

On presentation at the clinic, the dog was in sinus tachycardia (170 bpm) with a slightly weak but regular pulse and without audible murmurs. Other findings included relatively dry, pink mucous membranes, capillary refill time (CRT) 2.5 seconds, rectal temperature 38.6°C and mild dehydration. The superficial lymph nodes were palpably normal. There was firm, painful oedema on the left lateral abdominal wall, extending ventrally, affecting the sternal and preputial regions. Blood tests disclosed increased haematocrit (62%, reference range 37 to 55%), thrombocytopenia (142 × 10^3 platelets/μl; reference range 200 to 500 × 10^3 platelets/μl), elevated serum creatinine (165 μmol/l, reference range 50 to 110 μmol/l) and increased activity of alkaline phosphatase (243 IU/l, reference range 20 to 156 IU/l) and alanine aminotransferase (105 IU/l, reference range 21 to 102 IU/l). The leukocyte count was normal (12.91 × 10^3 leukocytes/μl, reference range 6.0 to 17.0 × 10^3 leukocytes/μl). In view of the thrombocytopenia, Polymerase Chain Reaction (PCR) and serologic testing was performed for *Anaplasma phagocytophilum*. The results obtained one week later revealed an antibody titer of 1 : 256 (cut off 1 : 128), although PCR was negative. Thoracic radiographs were unremarkable.

Fine-needle aspiration was performed on the skin lesion, cytological examination revealing many erythrocytes, neutrophils and an immense number of intra- and extracellular coccoid rods leading to a provisional diagnosis of a forming abscess. Symptomatic treatment was initiated for dehydration, pain and infection. Lactated Ringer's solution (RL) was administered at 10 ml/kg *i.v.* for the first hour, continuing at rehydration rate after supplementation with potassium chloride. Hydroxyethyl starch (HES 6%) 1 ml/kg/h *i.v.* was also administered over 24 hours. Analgesia was provided using methadone (Heptanon, Pliva Ljubljana) 0.2 mg/kg intramuscularly (*i.m.*) every five hours and car-

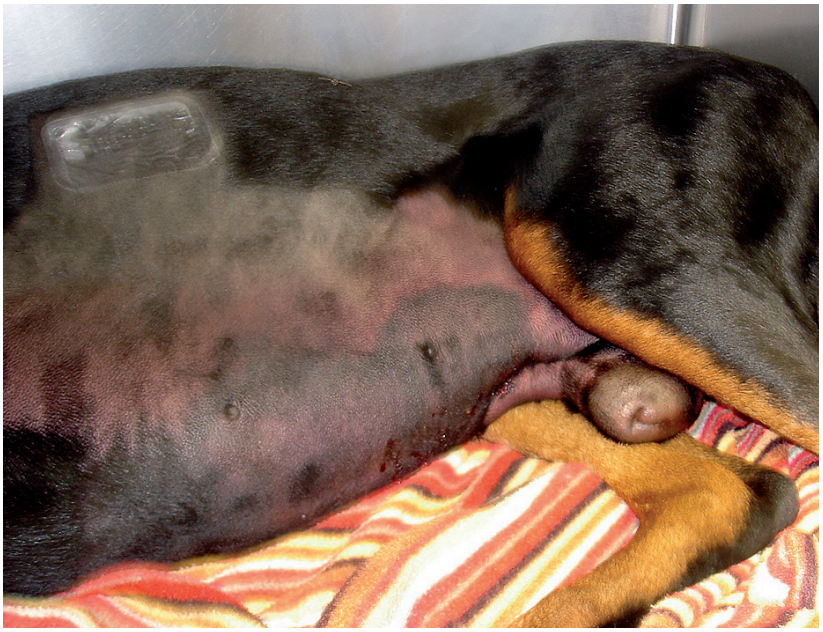

Figure 1. Ventral erythaema, demarcation line and transcutaneous serosanguineous discharge from the umbilical area

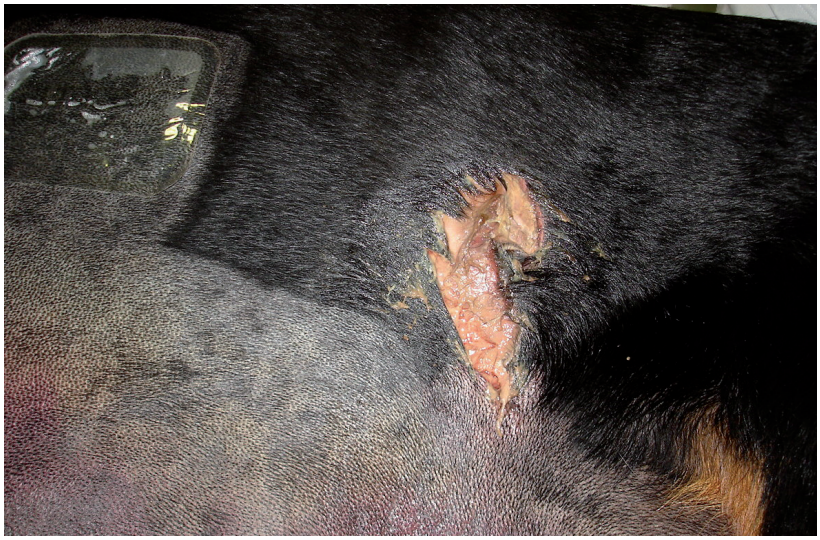

Figure 2. Necrosis at the subcutaneous injection site

profen (Rimadyl, Pfizer) 2 mg/kg *i.v.* twice daily; amoxicillin-clavulanic acid 20 mg/kg twice daily was administered orally to provide broad spectrum antibiotic cover.

The following day the leukocyte count had dropped (7.29 × 10^3 leukocytes/µl) and thrombocytopenia was more prominent (102 × 10^3 platelets/µl). Haemoconcentration was less pronounced (haematocrit 57%). That evening the skin of the ventral half of the body was erythaematous, with a distinct dark demarcation line around the ventral area. There was a transcutaneous serosanguineous discharge from the umbilical area (Figure 1). A fentanyl patch (Durogesic, Janssen Pharmaceutica NV) 100 µg/h was placed and gentamycin (Gentamicin, Krka) 5 mg/kg *i.m.* added once daily to extend the spectrum of antibacterial cover. The dog showed interest in food and water, and apart from one episode of postprandial vomiting, clinically relevant parameters were normal on the third day, so analgesic and antibiotic treatment was continued with addition of ranitidine (Ranital, Lek) 2 mg/kg *i.m.* and metoclopramide (Reglan, Alkaloid Skopje) 0.4 mg/kg *i.v.* every eight hours to minimise vomiting. The skin over the original injection site split late that evening discharging suppurative material with a putrid odour (Figure 2). This wound was surgically explored under general anaesthesia on the fourth day, with excision of necrotic skin and subcutaneous tissue. No connection was found between this and ventral oedema. A wet to dry bandage was placed with the aim of its replacement every 12 hours. The tooth extraction wound showed no signs of healing. Apart from traces of

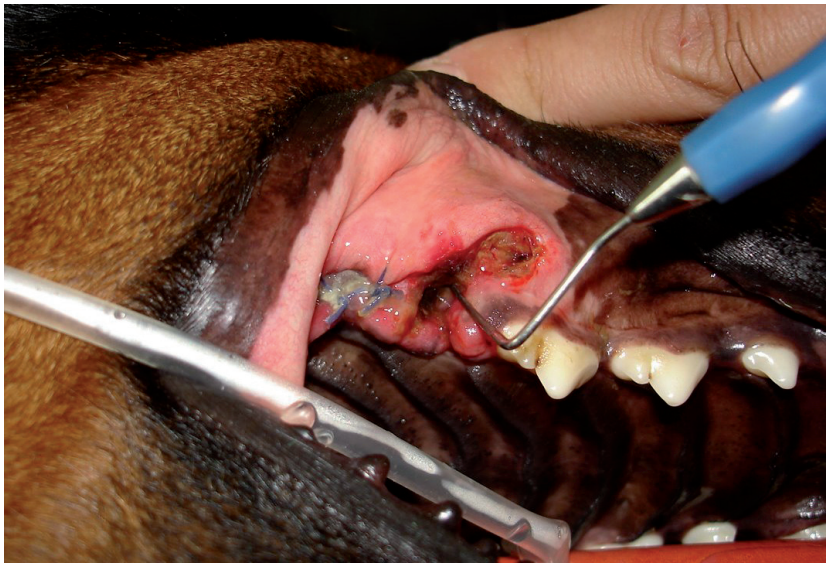

Figure 3. Six days after the extraction of maxillary right fourth premolar there was no evidence of healing at the extraction site. Alveolar osteitis ("dry socket") was suspected

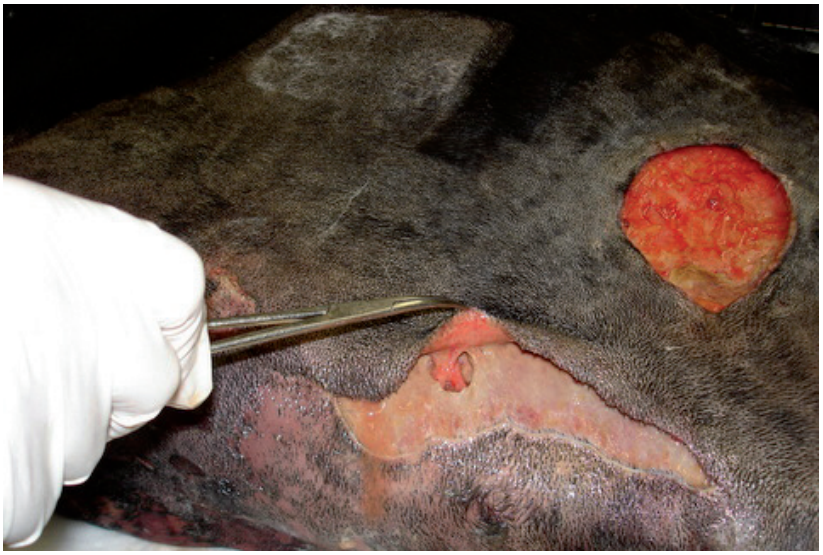

Figure 4. Six days into treatment. The surgically treated initial (near circular) skin slough at the site of the initial amoxicillin-clavulanic acid injection shows signs of wound granulation and healing but there is now skin separation ventrally. Much of the hair has depilated and the epidermis sloughed in the ventral region. This is most obvious in the lower left of the photograph below the hand and forceps

debris in the distal socket, the sockets were empty with areas of exposed bone and no ingrowth of granulation tissue (Figure 3). No retained root tips or other abnormalities were evident on dental radiographs of the area.

On the fifth day the dog was eating normally, it was bright with a body temperature of 37.6°C, normal heart rate, CRT and pink mucous membranes but the lesions were not shrinking so metronidazole (Efloran, Krka) 10 mg/kg *i.v.* twice daily was added to the previous treatment. When the bandage was replaced, hair depilated easily and the epidermis sloughed from the erythaematous ventral skin. Culture swabs were collected from an open wound that had appeared in the umbilical region. Isolated bacteria were identified as *S. marcescens* that showed sensitivity to ciprofloxacin, enrofloxacin, marbofloxacin, trimetoprim + sulphamethoxazole, gentamycin and cephotaxim, but were resistant to amoxicillin-clavulanic acid, cephalexin, cephalotin, clindamycin and metronidazole. No anaerobes were cultured.

The dog's appetite and general behaviour remained normal on the sixth day. Examination of the lesions revealed a well-demarcated skin slough extending from sternum to prepuce (Figure 4). Exploration demonstrated a lack of resistance of fascia to blunt dissection. Surrounding skin could be undermined to the level of costochondral junctions. The extent of the condition and the poor prognosis for repair in this location were discussed with the owner who elected for euthanasia and a full postmortem examination.

Necropsy revealed severe lesions of the skin and subcutaneous tissues of the ventral abdomen and thorax. The overlying skin had separated from the underlying fasciae, was necrotic and tore easily. Extensions containing pockets of turbid, brown foul smelling exudate radiated from the subcutaneous lesion along fasciae and fibrous septa between muscles. Severe acute lymphadenitis of the prescapular and axillary lymph nodes was present. Other findings included lack of evidence of healing at the extraction site, congestion of most parenchymal organs, atelectatic lungs with gross evidence of thrombosis surrounded by parenchyma haemorrhage, activation of sternal and costal bone marrow, mild hyperplastic and follicular gastritis, mucinous enteritis with mucosal oedema and acute haemorrhage. *S. marcescens* was isolated, typically in pure culture, from all samples of organs, lymph nodes, skin, muscles and the tooth extraction site.

Histopathology of the skin and subcutaneous tissues showed severe diffuse fibrinopurulent inflammation with a large number of degenerated immature neutrophils and macrophages expanding all along fasciae into superficial muscle fascicles of the pectoral and abdominal muscles. Blood vessels in the inflamed areas were dilated and plugged with fibrinous thrombi. The surrounding tissue was necrotic. Epidermis was missing in the necrotic areas of the skin and the surface was covered with abundant fibrinopurulent exudate containing numerous colonies of small coccoid bacteria. Histopathology of the lung revealed acute mild interstitial pneumonia. Liver showed acute toxic lesions with parenchymal degeneration, scattered necrotic hepatocytes and cholestasis with formation of biliary thrombi. The kidneys showed signs

of cholemic nephrosis consistent with the hepatic lesions, and mild chronic interstitial nephritis. Histological findings of other organs and tissues were consistent with the gross pathology.

DISCUSSION

Initial clinical findings of NF are reported to include localised erythaema, oedema and pain at the affected site (Naidoo et al., 2005). These signs were shown by the patient in the initial stages, however, fever, which is reported consistently (Jenkins et al., 2001; Naidoo et al., 2005; Worth et al., 2005), was not evident, so the initial differential diagnoses included cellulitis, lymphoedema and injection reaction, not fasciitis. Amoxicillin-clavulanic acid was chosen to provide initial broad spectrum, low toxicity antibacterial cover; allergy to it being considered unlikely.

The diagnosis of NF is based on the clinical signs and characteristic surgical findings; histopathology and culture of a recognised etiological agent helping confirm the diagnosis (Liu et al., 2005). Extensive tissue necrosis, intravascular thrombosis and moderate acute cellular inflammatory response are characteristic histopathological features of NF (Worth et al., 2005), these and extensive pathology at necroscopy were all detected in the case presented here, although the dog showed no clinical signs of organ failure. Skin sloughs, evident after about a week in this case, have been reported occasionally (Naidoo et al., 2005; Worth et al., 2005).

Only a few reports of NF have been published in the veterinary medicine. Mostly the infection is caused by *Streptococcus canis* (Prescott et al., 1997; DeWinter et al., 1999). *S. marcescens* as a cause of NF in immunocompromised humans has been recognised (Huang et al., 1999; Liangpunsakul and Pursell, 2001; Curtis et al., 2005). It does not appear to have been reported previously in a veterinary NF case though it has been isolated from intravenous catheters in dogs. The pathogenicity is considered to be low in healthy animals (Lobetti et al., 2002). The *A. phagocytophilum* infection, surgical stress and irritating subcutaneous injection might have caused a degree of debility increasing dog's susceptibility.

Necrotising fasciitis in humans is commonly a polymicrobial infection (Cunningham et al., 2001; Wong et al., 2003; Liu et al., 2005). As antibiotics had been administered prior to bacterial culture, it is not surprising that streptococci were not also cultured. Their absence does not exclude the presence of STSS, which is a well recognised complication of severe streptococcal infections (Naidoo et al., 2005), since other toxin producing bacteria, including enterobacteriaceae, may cause similar syndromes (Jenkins et al., 2001).

The initial source of the infection has not been confirmed. There were no visible signs at intravenous catheter sites and no obvious wound in the affected area, but the perioperative antibiotic injection had been given in that region. Skin contamination at injection sites (Fox et al., 1981) or even contaminated drugs may have been the source.

Enterobacteriaceae are frequently found as transient inhabitants of the oral cavity and pathological strains of *S. marcescens* have been found there in humans (Barbosa et al., 2006). Since the organism was present at the non-healing extraction site, it was a likely contributing factor to dry socket development (Van Cauwelaert de Wyels, 1998) and this might be the original site of infection. Bacteraemia is a recognised complication of oral surgery such as extractions (Nieves et al., 1997), so if the organism was involved in the endodontic infection, the resulting bacteraemia probably progressed to septicaemia with peripheral localisation to the skin.

Treatment of NF requires antimicrobial therapy, surgical debridement and delayed reconstruction (Naidoo et al., 2005). When there are concurrent signs of shock, aggressive supportive treatment is needed, i.e. intravenous fluids, plasma transfusions and nutritional support (Jenkins et al., 2001). Triple combination antibiotic therapy with penicillin, an aminoglycoside and metronidazole or clindamycin, which was also used in this case, is recommended for NF in man (Cunningham et al., 2001). Third-generation cephalosporins, fluoroquinolones or imipenem/cilastin are recommended for *S. marcescens* infections (Liangpunsakul and Pursell, 2001). The efficacy of enrofloxacin in dogs with NF has been questioned due to poor clinical responses despite in vitro bacterial sensitivity (Prescott et al., 1997). Treatment is complicated by the high incidence of multiple drug resistance (Liangpunsakul and Pursell, 2001), and only one of the drugs classically used for treatment of human NF showed in vitro efficacy in this case and it was not effective *in vivo*.

Delayed debridement due to late recognition is a major cause of mortality in people (Elliott et al., 1996; Wong et al., 2003; Liu et al., 2005), as are thrombocytopenia, liver dysfunction, low serum albumin (Liu

et al., 2005), elevated creatinine and lesions affecting the trunk (Elliott et al., 1996). Dog's initial thrombocytopenia, which worsened during the course of the disease, was ascribed to *Anaplasma* infection, although sepsis and disseminated intravascular coagulopathy will also have been factors (Jenkins et al., 2001; Naidoo et al., 2005). Other negative prognostic factors were present as well and in the end the tissue damage was so extensive that surgical repair following resection was considered impossible, leading to the decision to euthanise the dog.

In retrospect, oral surgery or injection site infection due to either primary drug contamination or massive irritation followed by vascular damage or thrombosis and secondary infection were the primary cause followed by bacteriemia, sepsis and shock with multiorgan failure, disseminated thrombosis and DIC. Bacterial culture of the initial cytology samples, aggressive fluid, intravenous antibiotic and nutritional treatment with surgical debridement should have been started immediately after the presentation, but even so, it is likely that there was already extensive severe tissue damage and multiorgan failure at that stage with guarded to poor prognosis.

Acknowledgement

We gratefully thank Dr. David A. Crossley (Animal Medical Centre Referral Services, Chorlton, Manchester, United Kingdom) and Dr. Michal Vlasin (Cardiothoracic Transplantation and Research, Mayo Clinic, Rochester, Minnesota, U.S.A.) for revising the manuscript.

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Received: 2008–10–08
Accepted: 2008–11–19

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