Streptococcus dysgalactiae subsp. equisimilis bacteremia in an HIV-1 patient with HBV/HCV co-infections: case report and literature review

Batteriemia da Streptococcus dysgalactiae subsp. equisimilis in un paziente con infezione da HIV-1 e coinfezione da HBV/HCV: caso clinico e revisione della letteratura

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INTRODUCTION

Until recent years, among clinically isolated β-haemolytic streptococci, Streptococcus pyogenes and Streptococcus agalactiae were considered the main pathogens in humans. In 1996, Streptococcus dysgalactiae subsp. equisimilis (SDSE) was proposed as a novel taxon among human-derived streptococcal isolates [1]. SDSE is a common pathogen in animals but it is generally considered a rare cause of infection in humans, even if it can be identified as a part of the usual flora of the nasopharynx, skin, genital and gastrointestinal tract. The immune status could play a role in SDSE infection appearance [2].

In the setting of the treatment of human immunodeficiency virus type-1 (HIV-1) infected patients, the introduction of combined antiretroviral therapy (cART) has dramatically changed the course and prognosis of the disease. As a result, the incidence of fatal opportunistic infections was significantly reduced and patients now live longer in a condition of relative immune suppression [3]. For these reasons new infectious agents may emerge and make difficulties in the management of HIV-1 infected subjects. Since the beginning of the AIDS epidemic, the occurrence of bacterial infections complicating the clinical course of HIV-1 disease has been recognized. Despite the degree of immunodeficiency (i.e. a CD4+ T cell count below 200/µl) represents the hallmark for the development of opportunistic infections in these subjects, several other factors may predispose HIV-1 infected patients to the occurrence of bacterial infections: they include abnormalities in humoral and cell-mediated immunity, phagocytic cells dysfunction, skin and mucous membrane defects [4].

Here we report a case of septic arthritis and soft tissue infection caused by SDSE in a patient with HIV-1 related immune deficiency and hepatitis B and C co-infections.

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CASE REPORT

A 59-year-old Caucasian man who have sex with men was admitted to the hospital because of the onset of high fever (up to 39.5°C) started from 3 days, and polyarthritis, without response to 48 hours therapy with amoxicillin/clavulanate (875/125 mg x 2/die) per os. He was known to be HIV-1 infected from 1988 (CDC Group B3). Main medical history included: hepatitis C (HCV) and B (HBV) co-infections with compensated liver cirrhosis, diabetes mellitus, chronic leukopenia and thrombocytopenia.

His past immunological history showed a CD4+ T cell nadir of 17% (215 cells/µl) in 1997 with HIV-1 RNA virus load of 42600 copies/mL, whereas CD4+ T cell count reached 418 cells/µl (20%) in 2003 with undetectable virus load (<50 copies/mL). He started antiretroviral therapy in 1991, initially with a zidovudine (ZDV) monotherapy and then with a combination of ZDV + didanosine (1994). In 1998, he started a protease inhibitor-based regimen that he is still taking, despite several changes due to toxicity and/or simplification. His cART always included lamivudine (3TC) and/or tenofovir difumarate (TDF) for the control of HBV infection.

Despite antiretroviral therapy, his platelet count always persisted below 50.000/mL. The last treatment included fosamprenavir 700 mg twice daily, and abacavir/3TC fixed dose, plus TDF 245 mg, both once daily.

At the hospitalization time, the patient appeared very sick. Physical examination revealed a body temperature of 40°C, a pulse rate of 128 bpm, a 74.4 kilograms body weight, and the presence of acute arthritis with painful movements, tenderness and swelling of left ankle and right wrist and shoulder joints. Moreover, several cutaneous phlegmons were present.

As anamnestic feedback he reported a previous exposure to domestic animals (two dogs and one ferret) and referred a cutaneous scrape between the IV and V toe of the left foot occurred a few days before the symptoms’ onset.

Echocardiography, chest x-ray, abdominal ultrasound and Doppler ultrasonography of the lower limbs were normal. Laboratory evaluation showed leukocytosis (white cell count 13860/mL with neutrophils 80% and lymphocytes 8.6%), CD3+ T cells 64% (763/µL), CD4+ T cells 16% (191/µL), platelet count 110000/mL, erythrocyte sedimentation rate (ESR) 39 mm/h, lactate dehydrogenate 600 U/L, cholinesterase 2000 U/L, serum albumin 2.5 gr/dL. RPR and TPHA were negative. Blood and synovial liquid cultures were taken. Waiting the culture results, the patient was initially treated with ciprofloxacin 500 mg every 12 hours and minocycline 100 mg every 12 hours, both as oral administration. His clinical conditions did not improve and he underwent to a new check-up.

Total white blood count was 18000 cells/mL and platelet count increased to 270000/mL. Five days after the admission, a blood culture yielded a -hemolytic group C Streptococcus, further identified as SDSE, using a BBL™ Crystal™ Identification System (Becton, Dickinson and C., NJ, USA). Synovial fluid did not show any bacterial growth.

According with the susceptibility testing (BBL™ Sensi-Disc™ Susceptibility Test Discs, Becton, Dickinson and C., NJ, USA), that showed a broad spectrum of antibiotic activity, the antimicrobial treatment was switched to intravenous (i.v.) amoxicillin/clavulanate 1000/200 mg every 8 hours plus i.v. teicoplanin 400 mg x 2/die the first day, then 400 mg every day. Teicoplanin was added due to the lack of response to the previous amoxicillin/clavulanate oral dosing.

His conditions rapidly improved and within ten days the resolution of fever, arthritis and cutaneous phlegmons was achieved, together with the normalization of laboratory parameters (ESR dropped to 26 mm/h, WBC decreased to 3980 cells/µL, with neutrophils 71% and lymphocytes 17%, platelet count was 250000/µL). The i.v. therapy was stopped after 10 days, and followed by the amoxicillin/clavulanate (875/125 mg x 2/die) oral dosing for other 10 days. The patient was discharged after 2 weeks from the start of the i.v. treatment. After 4 weeks, laboratory evaluation confirmed the stabilization of inflammatory indexes (ESR, WBC count), whilst platelet count gradually began to decrease (180000/mL) and after 8 weeks their number came back below 50000/mL.

DISCUSSION

Streptococcus dysgalactiae subsp. equisimilis (SDSE) belongs to the group of pyogenic streptococci also referred as β-hemolytic streptococci. SDSE was proposed in 1996 as a new taxon.
involved in human streptococcal infections. According to recent taxonomic studies, large colony-forming groups C and G streptococci that infect humans are classified as SDSE, previous belonging to Lancefield group C and G [5-7]. SDSE is commonly a pathogen in animals and may be identified as part of the human flora in the upper respiratory, gastrointestinal and female genitourinary tracts; it is often recognized in skin lesions [8, 9].

SDSE infections spread from person-to-person and the majority of infections are community-acquired. In fact, the microorganisms are largely disseminated by aerosols from the nose and throat of infected people or spread through direct contamination of wounds. Infections can be endogenous (from organisms located on skin or mucous membranes) or exogenous (from animal sources). SDSE can colonize healthy humans and represent the major Group C β-hemolytic streptococcus involved in several localized human infections including pharyngitis, pyoderma, cellulitis, wound infections, abscesses, erysipelas and necrotizing fasciitis [8, 9]. Severe invasive infections often occur in predisposed hosts: in fact they are common in patients affected by underlying immunodeficiency predisposing diseases or conditions such as age (neonate or elderly), diabetes mellitus, HIV-1 disease, alcoholism and injection drug use, and also in patients with chronic cardiovascular diseases and in those undergoing chemotherapy or affected by cancer [10]. Invasive infections include arthritis, osteomyelitis, pneumonia, peritonitis, abdominal and epidural abscesses, meningitis, endocarditis, puerperal septicemia, neonatal infections, myositis and streptococcal toxic-like syndrome [11]. The number of patients with invasive infections, mainly exhibiting bacteremia with SDSE, are now increasingly observed worldwide.

Review of literature shows that SDSE infections are the most frequent ones among all Streptococcus groups. Bradley et al. examined Group C streptococci bacteremia cases, reporting that 75% of the affected patients had an underlying serious clinical condition: 20.5% had a cardiovascular disease (coronary, valvular, or peripheral disease); 14.8% had immunodeficiency following chemotherapy, radiotherapy, hypogammaglobulinemia, corticosteroid therapy or splenectomy; 20.5% had cancer [12]. Stein et al. reported a pyogenic arthritis by *Streptococcus equisimilis* in a patient affected by AIDS who received corticosteroid therapy for severe atopic dermatitis. The corticosteroid immune-suppression determined a worsening in HIV-1 disease that may have played a role in the development of the *Streptococcus equisimilis* infection [13].

Group C streptococci infections are often associated with exposure to animals. In some cases direct exposure to ill animals preceded bacteremia, whilst in others the infection is associated with the animal products contact. Food-borne outbreaks of Group C streptococcal infections have been described after the ingestion of unpasteurized milk from cows or goats colonized by *Streptococcus zooepidemicus* [14, 15]. Human skin colonization with SDSE is common and the microorganism has been identified as responsible for various cutaneous and subcutaneous infections.

Skin injuries and soft tissue damage may provide a portal of entry, leading to bacteremia [16, 17]. Bradley et al. reported that only 17.1% of bacteremia due to Group C streptococci are caused by visible skin lesions whilst the most common source of infection was represented by the respiratory and the gastrointestinal tracts (20.5% and 18.2% of cases, respectively) [12]. Also Mohr and Skogberg in patients affected by bacteremia have shown the presence of a cutaneous site of entry in 17% and 33% of cases, respectively. In 38.6% of cases, the source of infection cannot be identified.

A case-control study conducted in Finland in patients hospitalized for acute bacterial cellulitis showed that SDSE was found most often and it was isolated from 22% of patient samples of either skin lesions or blood. A skin lesion was observed in a large number of patients who developed cellulitis [18]. Takahashi et al. reported that 13 elderly patients developed severe invasive infections with SDSE and 10 subjects had underlying diseases including neurologic disorders and diabetes mellitus [2]. According to their experience, doctors treating elderly patients should keep in mind invasive infections caused by SDSE as differential diagnosis, mainly if an underlying illness is present. In a retrospective observational study in Taiwan, SDSE was the most common microorganism identified in 86/92 patients with Group G streptococcal bacteremia [19].

In a retrospective population-based study on adult patients Rantala S. et al. identified 128 cases of bacteremia due to SDSE: incidence of
SDSE increased during the study period, with the disruption of cutaneous integrity as a common predisposing factor and the presence of skin lesions as initial clinical manifestation of bacteremia [20]. Broyles L. et al. performed a population-based surveillance for invasive disease due to □-hemolytic streptococci: on a total of 489 cases of invasive infections, 212 were caused by SDSE, 87% of patients had underlying diseases and these were more common among subjects with SDSE invasive infections [21]. In older patients the main clinical manifestations of SDSE disease were skin and soft-tissue infections.

According to literature, our patient was immunosuppressed by HIV-1 infection and had other underlying conditions that predispose him to the development of systemic infections, such as diabetes, liver cirrhosis and leukopenia. Moreover, additional favoring conditions were present such as the exposure to pet animals and a skin wound that may have represented the site of entry for the pathogen. During the acute phase of the bacterial disease, a transient improvement in platelet count has been observed, lasting for about 6 weeks and then decreasing to the initial levels.

Thrombocytopenia is often associated with HIV-1 infection and it is associated with the presence of immune complex or serum anti-platelet antibodies.

Generally, the majority of patients with HIV-1-related thrombocytopenia may increase their platelet count during cART. This can occur also during acute infections: in fact, a HIV-1 patient who transiently resolved thrombocytopenia during an acute episode of Pneumocystis jirovecii pneumonia has been described [22]. HIV-1 uninfected subjects with chronic thrombocytopenia can occasionally have a transient elevation of platelet count during acute bacterial infections, that reaches a maximum within 2 weeks after the infection onset and then decreases to the initial level when the infectious episode recovered [23-25].

Different mechanisms have been suggested for this increase, such as production of endogenous interferon, stimulation of thrombopoiesis by cytokines (IL-1, IL-6 and IL-11), reticulo-endothelial receptors blocking by the immune complex produced during infections [22, 24]. Probably the same mechanisms have been involved in the transient platelet increase observed in this patient.

In the last years, epidemiological studies have demonstrated an increased number of infections caused by SDSE, and that the immune status plays an important role in the appearance of this pathogen. However, as already reported in several cohorts, our case suggests SDSE as a quite rare bacterial pathogen during HIV-1 infection. In fact, despite invasive SDSE infections are often described in several immune suppressive conditions and in subjects with underlying co-morbidities such as diabetes, alcoholism, neoplastic and hematologic diseases or in conditions such as elderly or skin breakdown, they rarely appear associated with HIV-1 disease [12, 13, 26-29]. This rare incidence could be explained by the absence (or less relevant) impairment of the phagocytic cells function in HIV-1 infected subjects, compared to other immune deficiency conditions. In our patients, as well as in other HIV-1 infected subjects in which SDSE infections have been described, a relevant role has been exerted by the presence of a site of entry for the pathogen, the foot scrape, with the disruption of the cutaneous barrier. According with the increased numbers of people living with diseases or conditions associated with an immune suppressive disorder, SDSE will probably achieve even more relevance and clinical importance in the management of medical and surgical diseases. It is mandatory to have an increased awareness of emerging SDSE infectious episodes in order to identify them in cases of bacteremia and/or severe infections and to develop strategies for future vaccination approaches in selected categories.

Conflict of interest declaration
The authors declare they have no competing interests.

Keywords: Streptococcus dysgalactiae subspecies equisimilis, HIV-1 infection, bacteraemia, septic arthritis, cellulitis, HBV/HCV co-infection.
**SUMMARY**

*Streptococcus dysgalactiae subspecies equisimilis* (SDSE) is a common pathogen in animals and generally considered a rare cause of infection in humans. Recently, epidemiological studies demonstrated an increasing number of severe infections, including bacteremia and endocarditis, caused by SDSE, mainly in predisposed hosts, immunocompromised by underlying conditions. Even though the immune status seems to play an important role in the appearance of SDSE infections, this microorganism has been rarely described as a pathogen in HIV-1 infected subjects. An extensive review of the literature on this pathogen is reported, with a description of a case of SDSE bacteremia associated to septic arthritis with soft tissue infection in a patient with HIV-1 disease and chronic hepatitis due to HCV and HBV co-infections.

**REFERENCES**


