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Rassegna

Review

Streptococcus anginosus group disseminated infection: case report and literature review

Infezione disseminata da microrganismi del gruppo Streptococcus anginosus*: caso clinico e rassegna della letteratura*

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INTRODUCTION

The *Streptococcus anginosus* group includes three taxonomically distinct species: *Streptococcus anginosus*, *Streptococcus intermedius* and *Streptococcus constellatus* [1]. The term "*Streptococcus milleri* group" has been also frequently used to refer to such a group [2]. *S. constellatus* can be further subdivided in two subspecies: *S. constellatus* subsp. *constellatus* and *S. constellatus* subsp. *pharyngitis* [3]. Virtually all strains (93%) of *S. intermedius* are non hemolytic (alpha- or gamma-hemolysis), while 38% of *S. constellatus* and 12% of *S. anginosus* are β-hemolytic [2]. Members of the *S. anginosus* group are commonly found as commensal of the oropharyngeal, gastrointestinal and genitourinary flora, but they can become pathogenic and cause contiguous or distant infections after mucosal damage [4, 5]. These organisms can be responsible of pyogenic invasive infections with abscess formation, but are a very infrequent cause of infective endocarditis (IE) compared to other streptococci [2, 6-9].

S. intermedius is more commonly isolated from brain and liver abscesses, whereas *S. constellatus* and *S. anginosus* show a wider distribution with urogenital, pleuropulmonary and gastrointestinal involvement [2, 10].

In this paper, we describe a case of a highly disseminated pyogenic infection caused by *S. intermedius* affecting the brain, the lung, the liver and the pleural cavity. We also provide an extensive literature review of disseminated invasive infections sustained by members of the *S. anginosus* group. Because of the uniqueness of our patient and since there are very few reports of disseminated *S. anginosus* group infections, we believe this work might be of some interest for Infectious Diseases and Internal Medicine practitioners.

CASE REPORT

A 61-year-old man was admitted to the hospital because of fever, right upper quadrant abdominal pain and myoclonic seizures with left arm paresis. On admission, the body temperature was 36.8°C, the blood pressure 139/70 mmHg, the pulse rate 70 beats per minute and the oxygen saturation 97% while he was breathing room air. Physical examination revealed right upper quadrant tenderness with no distension and moderate hepatosplenomegaly. No evidences of dental caries, periodontitis, or oral abscesses were found.

Hematologic and serum chemical laboratory data showed a white blood cell count of 16,580/µl (differential count: 86% neutrophils, 7% lymphocytes, 0.3% eosinophils), normocytic and normochromic anemia (hemoglobin of 8.5 g/dl), platelet count of 528,000/µl, C-reactive protein (CRP) of 30,000 µg/l (reference range [RR] 100-6000 µg/l), ferritin plasma levels of 1189 µg/L (RR 30-400 µg/l), fibrinogen of 11.59

g/l (RR 1.5-4.00 g/l) and erythrocyte sedimentation rate of 120 mm/hr. Liver function tests, blood urea nitrogen and electrolytes were within reference ranges.

The patient underwent an immediate imaging evaluation. A full-body computed tomography (CT) scan revealed a rounded lesion with central necrosis and surrounding oedema in the right frontal lobe of the brain. Two excavated pulmonary lesions with air-fluid levels were shown (Figure 1): one (9 cm by 8 cm), with both pleural contact and perihilar extension, in the right middle lobe and the other one (2 cm) in the left lower lobe. Also, a right-sided, small (3.2 cm by 1.5 cm) pleural empyema with loculations was observed, along with two little hypodense lesions, with mild enhancement after contrast injection, localized in the fourth (2.2 cm) and, respectively, the eight (1.2 cm) hepatic segments. A magnetic resonance imaging (MRI) of the brain showed a hyperintense ring-enhancing lesion (3.5 cm in diameter) with perilesional oedema (Figure 2). No heart valve vegetations were seen on transesophageal echocardiogram (TEE) and Human Immunodeficiency Virus (HIV) serological tests were performed and later proved to be negative.

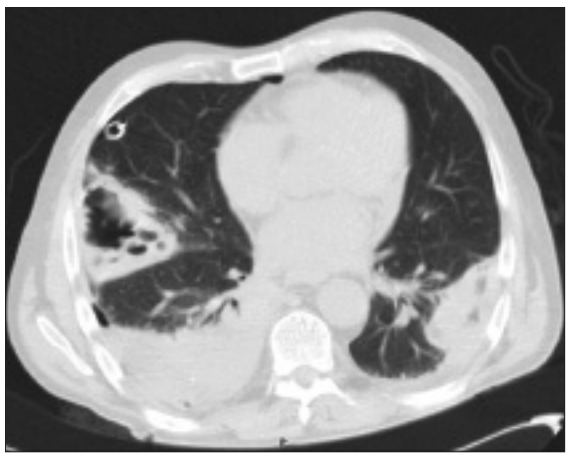

Figure 1 - Chest CT scan showing two cavitated lesions with air-fluid level in the right middle lobe and in the left lower lobe respectively. A right-sided pleural empyema with loculations is also well documented.

Because of arising suspicion of disseminated pyogenic infection, bronchoalveolar lavage (BAL) fluid and three blood samples were sent for cultures. Microbiologic identification tests (Vitek 2, bioMérieux, Marcy l'Etoile, France) of BAL fluid and blood culture growth revealed *S. intermedius*. Furthermore, a frontotemporal craniotomy and surgical drainage of the brain lesion were performed and the same organism was isolated from the purulent material drawn.

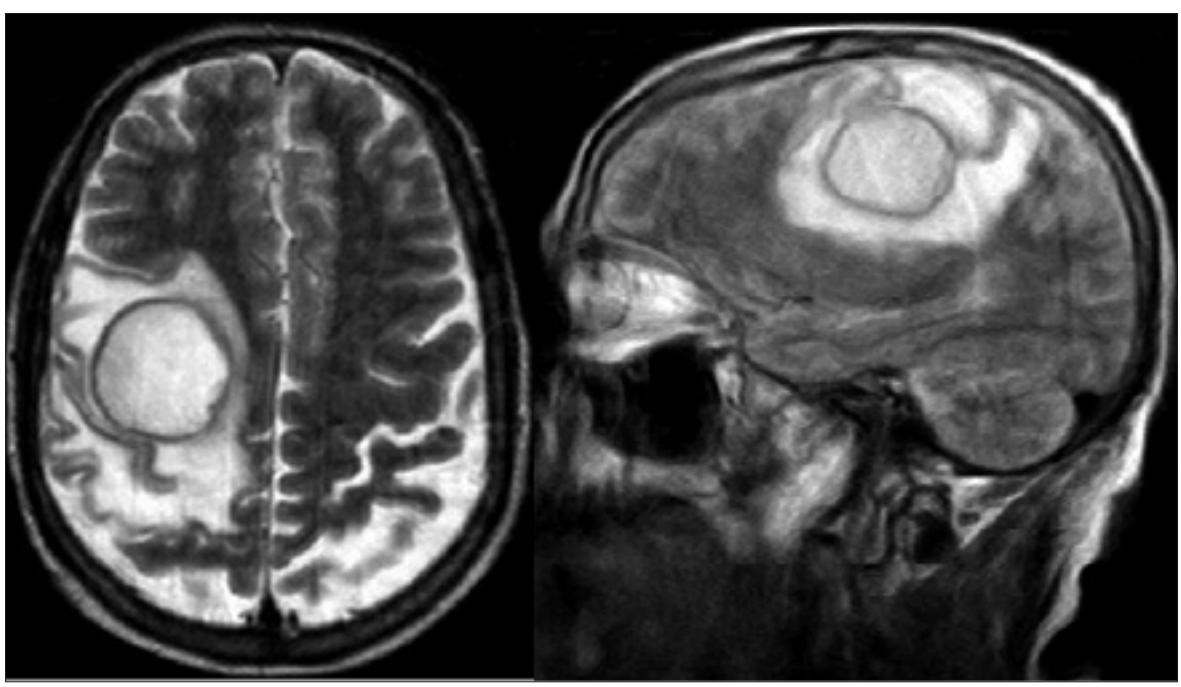

Figure 2 - MRI of the brain showing a hyperintense ring-enhancing lesion (3.5 cm in diameter) with perilesional edema. Left, axial view; right, sagittal view.

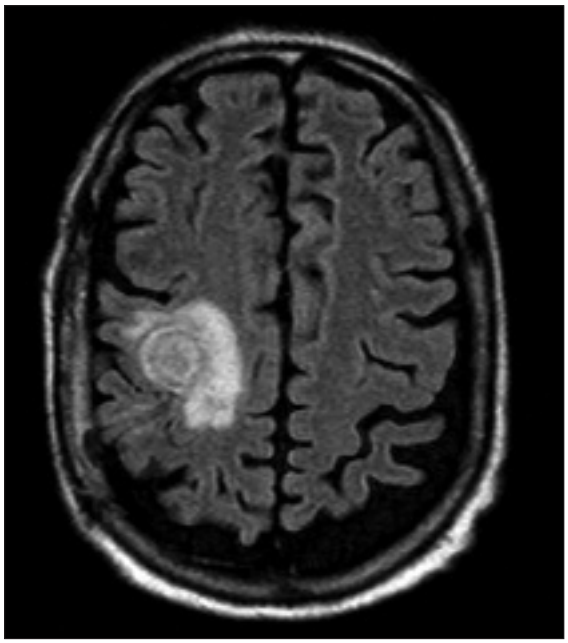

Figure 3 - MRI of the brain showing lesion improvement after a 10-week course of antimicrobial chemotherapy.

Based on microbiological results, initial empirical antimicrobial treatment regimen with meropenem, trimethoprim/sulfamethoxazole and voriconazole was changed to IV ceftriaxone 2 g b.i.d. After a six-week course of intravenous antibiotic therapy, the patient achieved a near-complete neurological recovery and was therefore shifted to chronic oral amoxicillin (4 g/day in four divided doses). Two months after ceftriaxone withdrawal, chest CT scan and brain MRI (Figure 3) showed marked improvement of lung and brain lesions, respectively. Because of persistence of empyema, slowly responding to antibiotic treatment, the patient was switched to chronic antimicrobial therapy with oral amoxicillin.

MATERIALS AND METHODS

We performed a literature search with PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) to identify studies reporting cases of disseminated pyogenic infection sustained by *S. anginosus* group species. Disseminated pyogenic infections were defined as single or multiple abscess formation involving two or more of the following organs or systems: central nervous system (CNS), lung, liver and spleen. We used the terms "*Streptococcus milleri*", "*Streptococcus anginosus*", "brain abscess", "pulmonary abscess", "liver abscess" and "splenic abscess" and we limited our search to case reports published in English language. Most of results were obtained using "*Streptococcus milleri*" instead of "*Streptococcus anginosus*". The latter yields just a very few case reports which were included in our analysis. Search queries were as following:
Streptococcus milleri AND brain abscess AND pulmonary abscess AND liver abscess: no results found.
Streptococcus milleri AND brain abscess AND pulmonary abscess: we found 8 results and we included 4 of them in the review. The three works discarded referred to particular cases not matching criteria of our definition.
Streptococcus milleri AND brain abscess AND hepatic abscess: we included 5 results fulfilling the criteria of our definition.
Streptococcus milleri AND pulmonary abscess AND hepatic abscess: we found one work reporting the case of a hepatopulmonary hydatid disease with superimposed *S. milleri* infection. The paper was not included in the review.
Streptococcus anginosus AND brain abscess AND splenic abscess: one result included in the review.
We also included a case presented by Petti *et al.* describing a patient with lung and multiple intracerebral abscesses due to *S. constellatus* [11].

RESULTS

PubMed search yielded 11 well documented cases of disseminated pyogenic infections sustained by *Streptococcus* species belonging to *S. anginosus* group. One case with disseminated pyogenic infection reported by Melo et al. was not included in our analysis because patient therapy and clinical course were not well documented: clinical improvement would have oddly occurred after a treatment of 3 weeks with oxacillin and gentamicin, but there are no evidences for *S. anginosus* group oxacillin susceptibility in literature [12]. According to our definition, brain has demonstrated to be almost always affected with various combinations of concomitant lung, liver and spleen involvement. Patient underlying conditions, etiologic agents isolated, antimicrobial chemotherapy treatment regimens employed are shown in Table 1.
We analyzed the clinical features of 12 patients, including the case reported in this paper.

Tabella 1 - Case reports of disseminated pyogenic infections caused by *S. anginosus* group. NR = not reported; W = week(s).

Reference	*Patient n°/age (y)/sex*	*Underlying conditions*	*Previous antimicrobial treatments*	*Etiologic agents*	*Blood cultures*	*Endocarditis*	*Brain*	*Lung*	*Liver*	*Spleen*	*Other*	*Antimicrobial therapy after diagnosis*	*Outcome and follow-up*
Melo et al., 1978 [12]	1/69/M	Atherosclerotic heart disease, mild hypertension, lumbar laminectomy (2 weeks before)	NR	*S. intermedius*	✓	✓ (persistently positive blood cultures)	✓ (multiple)	(single)	✓			*Hepatic abscess*: surgical drainage + IV chloramphenicol (1W) followed by penicillin per os *Brain abscess*: surgical drainage + IV penicillin G + chloramphenicol	Deceased
De Moor et al., 1985 [47]	2/10/M	NR	NR	*S. milleri*			✓ (single)		✓ (multiple)			7W IV penicillin + metronidazole + chloramphenicol + clindamycin	Healed, 6th cranial nerve palsy (7W)
Mofredj, 1999 [21]	3/60/M	COPD, tooth cavities	NR	*S. anginosus*	✓		✓ (multiple)		✓ (multiple)			6W IV amoxicillin (2g q.i.d) followed by 1 month amoxicillin per os 2 g q.d.	Healed, right hand paresis (5 months)
Velghe et al., 2004 [20]	4/69/M	Respiratory tract infection, endophthalmitis	IV co-amoxi clav (1 g q.i.d.)	*S. milleri*	✓		✓ (single)	✓ (multiple)				9W IV penicillin G (24 MU q.d.) + clindamycin	Healed (NR)
Lee et al., 2005 [48]	5/58/M	Total left hip arthroplasty	IV ceftriaxone, vancomycin, metronidazole, ampicillin, acyclovir, IV dexamethasone	*S. anginosus*	✓		✓ (multiple)		✓ (single)		Periprosthetic abscess	IV ceftriaxone + arthroplasty removal + extraventricular drainage + hepatic drainage	Deceased
Wagner et al., 2006 [49]	6/39/NR	Several periodontal lesions, periodontitis	NR	*S. intermedius*	✓		✓ (multiple)		✓ (single)			Surgical drainage of hepatic abscess + ceftriaxone IV + metronidazole followed by penicillin G + metronidazole. After 7 days surgical drainage of cerebral abscesses + scaling of infected pockets and extraction of nine teeth	Healed, almost complete restored function of the 7th cranial nerve (3W)
Hoshino et al., 2006 [50]	7/56/F	Cavernous sinus thrombosis, marked stenosis and aneurysmal formation of the right internal artery in the intracavernous portion	NR	*S. constellatus*	✓		Subarachnoid abscess	✓ (multiple)				7W IV ampicillin/sulbactam 9 g/die	Healed, residual lateral gaze palsy (6 months)
Petti et al., 2008 [11]	8/16/M	NR	Vancomycin + ceftriaxone + acyclovir	*S. constellatus*			✓ (multiple)	✓ (single)				Vancomycin + ceftriaxone + metronidazole + partial lobectomy followed by 16 W ceftriaxone + rifampin	Residual behavioral abnormalities (NR)

follow **Tabella 1 -** Case reports of disseminated pyogenic infections caused by S. anginosus group. NR = not reported; W = week(s).

Reference	*Patient n°/age (y)/sex*	*Underlying conditions*	*Previous antimicrobial treatments*	*Etiologic agents*	*Blood cultures*	*Endocarditis*	*Brain*	*Lung*	*Liver*	*Spleen*	*Other*	*Antimicrobial therapy after diagnosis*	*Outcome and follow-up*
Erne et al., 2010 [51]	9/61/M	haemoptysis		*S. intermedius*			✓ (multiple)	✓ (single)				1 year antimicrobial therapy + pulmonary lobectomy	Healed (33 months)
Maliyil et al., 2011 [52]	10/21/M	NR	NR	*S. intermedius*	✓		✓ (multiple)				✓ (single)	Surgical drainage of splenic abscess + 2W IV ceftriaxone 2 g q.d. and vancomycin followed by a second surgical drainage of splenic abscess + IV ceftriaxone 2 g b.i.d. and vancomycin followed by 6W ertapenem	Healed (4 months)
Russell et al., 2011 [53]	11/51/M	NR	Amoxicillin + clarithromycin followed by IV co-amoxiclav, flucloxacillin and metronidazole	*S. milleri*			✓ (single)	✓ (single)			Spondylodiscitis T4-T5	Surgical drainage + 4W IV benzypenicillin + metronidazole + 2W antimicrobial therapy per os	Near full recovery (NR)
Present case report	12/61/M	Closed angle glaucoma, emphysema, diverticulosis, abdominal aortic ectasy	Meropenem + trimethoprim/ sulfamethoxazole + voriconazole	*S. intermedius*	✓ (single)		✓ (multiple)	✓ (multiple)			Pleural empyema	Surgical drainage + 6W IV ceftriaxone 2 g q12h	Near full recovery (ongoing)

Demographic features

We found evidence of a high prevalence (83%) of male patients, greatly exceeding that (8%) of female patients.

The gender of one patient was not reported. Mean age of patients was 47.58 years with a standard deviation of 20.92 years.

Underlying conditions

In cases included in our review, underlying conditions were reported for 8 patients, with dental infections, malignancy, gastrointestinal and respiratory tract diseases accounting globally for 42% of cases.

Infective endocarditis

Even though positive blood cultures were reported in 67% of cases, no definite endocarditis was encountered. The case highlighted in Table 1 could be more properly defined as possible endocarditis, according to modified Duke criteria [13].

Site of Infection

Brain was affected in almost all cases reviewed, with a prevalence of 92%. Concomitant brain-liver, brain-lung and brain-spleen involvement occurred in 50%, 42% and 8% of cases respectively. One patient (8%) had multiple pulmonary abscesses and a subarachnoid abscess. The patient presented in this paper was remarkably characterized by the presence of multiple pyogenic manifestations in four different sites (brain, lung, liver and pleural cavity). To our knowledge, this is the only documented case reported in literature of such a great extent of dissemination of an invasive infection sustained by a member of the *S. anginosus* group.

Microbiology

Microbiological identification tests revealed the presence of *S. intermedius* in 42% of patients, while frequencies of *S. anginosus* and *S. constellatus* were 17% each. In 3 cases (24%) the etiologic agent was generically referred to as *S. milleri.*

Therapy
Antimicrobial therapy generally took no less than six weeks. Ninety-one percent (91%) of patients were treated with β-lactam antibiotics (penicillin, amoxicillin, ceftriaxone, ampicillin/sulbactam, ertapenem). The antimicrobial treatment was not reported in one case. Chloramphenicol was added to the antimicrobial regimen in 2 (17%) patients, metronidazole in 4 (33%) patients, clindamycin in 2 (17%) patients, vancomycin in 2 (17%) patients and rifampin in 1 (8%) patient. Surgical drainage was performed in 50% of cases. In two patients partial brain lobectomy and pulmonary lobectomy were required, respectively,

Outcome
Two (17%) patients died, the remainder showed a full or near-full recovery after an appropriate antimicrobial treatment. Interestingly, 66% of patients whose improvement was complete received surgical treatment along with medical therapy, and 66% of patients with partial recovery had no surgical procedures performed.

DISCUSSION

S. anginosus group strains are able to cause brain abscesses with at least two different pathogenetic mechanisms. The first one is represented by direct spread from a contiguous cranial site of infection such as paranasal sinusitis, otitis media, mastoiditis, meningitis, orbital cellulitis and odontogenic infection, with community acquired sinusitis and mastoiditis being the most epidemiologically important [5, 14-17]. A significant proportion of brain abscesses are a complication of head trauma or neurosurgery with wound infection and subsequent development of cerebritis [15, 16, 18]. The second mechanism is the result of haematogenous spread from a remote site such as gastrointestinal or respiratory tract with bloodstream infection (BSI) as a source of inoculums [12, 19-21]. Intracranial extension of an infection from a contiguous site has the tendency to appear as a single abscess, while CNS invasion through the bloodstream cause formation of multiple abscess. In cases described in this paper, *S. anginosus* group propensity to cause pyogenic infections through bacteraemia and haematogenous dissemination is well demonstrated by the high prevalence of multiple abscesses in the same organ or system and by the multi-organ involvement (brain and, to a lesser degree, liver, lung and spleen). Moreover, there are several medical illnesses that may play an additional role in infections caused by *S. anginosus* group such as liver cirrhosis, malignancy, diabetes mellitus [7, 16, 22, 23].
Unlike other viridans streptococci, *S. anginosus* group members exhibit specific virulence factors that are likely to be implicated in the well-recognized ability to cause invasive pyogenic processes [7, 8, 25, 26]. In order to bring about an abscess, bacteria must attract polymorphonuclears (PMNs) and resist phagocytosis and killing [27]. Compared to *Staphylococcus aureus*, with its well documented capacity to cause abscesses, *S. anginosus* group strains show even increased survival after ingestion by PMN's [27]. Also, *S. aureus* is able to inhibit ingress of PMN's, in contrast to viridans streptococci whose reduced tendency to abscess formation is associated with a higher degree of chemotaxis [27]. *S. aureus* Panton-Valentine leukocidins are thought to be responsible of chemotaxis inhibition and abscess pathogenesis: by damaging PMNs and by delaying their ingress, leukocidins provide invading bacteria with an advantage [27]. *S. intermedius* produces a leukocidin-like intermedilysin, whereas *S. constellatus* and *S. anginosus* display other toxins that may exert a leukocidin-like effect [27, 28]. Differences in virulence factors between members of the *S. anginosus* group might be partly responsible for the marked predominance (45% in our review) of *S. intermedius* isolation from brain abscesses [10]. In addition, *S. anginosus* group species possess thrombin-like activity and the ability to bind to platelet-fibrin clots by the use of a combination of fibrinogen and fibronectin binding mechanisms, protecting themselves from antibodies and immune effectors [29].
Notwithstanding *S. anginosus* group strain ability to cause abscesses, they are considered to be a very rare cause of infectious endocarditis (IE) [9]. Along with β-hemolytic streptococci, they account for 5% to 7% of these latter infections [8]. Potential adherence to extracellular matrix (ECM) is not the same in different *Streptococcus* species as demonstrated by a survey of streptococcal isolates from patients with endocarditis conducted by Tart et al. [30]. Ability to bind to ECM decreases progressively from high binders (*S. mutans* then *S. sanguis*) to low binders (*S. mitis* then *Enterococcus faecalis*) [30].

Authors found extremely low binding ability in *S. aureus* isolates and no adherence in *S. anginosus* isolates [30]. These data are concordant with evidences reported by a previous work of Scheld *et al*., in which adherence ratios to fibrin and fibrin-platelet matrix *in vivo* were shown to be directly correlated with dextran produced in broth cultures, with *S. mutans* and *S. sanguis* ranking first and second respectively [31]. Not surprisingly, we found a single (8%) patient with merely possible endocarditis and this means that the pathogenetic mechanism of multiple organ involvement in suppurative *S. anginosus* group infections can be attributed to septic embolization only in a very few cases, if at all.

Taking into account literature reports, antimicrobial treatments employed in patients analyzed in this review proved to be appropriate in almost all cases. Nearly all isolates of *S. anginosus* group are susceptible to amoxicillin and penicillin, even though a few penicillin-resistant infections have been encountered [8, 32, 35]. Of interest, the organism may be resistant to daptomycin and recently a *S. anginosus* breakthrough bacteremia associated with septic shock has been described in a patient receiving this antibiotic [36]. Although not definitely demonstrated, some authors suggest initial combination therapy with penicillin and an aminoglycoside, mainly because tolerance may be found in some isolates [8, 37-41]. In addition to parenteral antimicrobial therapy, treatment of an abscess involves drainage of purulent material or surgical excision [42]. Medical therapy alone should be reserved for patients with multiple and/or small, well defined lesions or when patients are at high risk for surgical complications [15, 43, 44]. Intensive antimicrobial therapy cannot substitute surgical treatment, because there is a wide fluctuation in antibiotic penetration into abscesses, especially brain lesions, and this variation is partially independent of dose given [15, 45].

CONCLUSIONS

We have reported a unique case of *S. anginosus* group bloodstream infection (BSI) with multiple brain, hepatic and pulmonary pyogenic lesions. Analysis of our patient as well as literature review reveal the ability of members of the *S. anginosus* group to cause disseminated bacteremic invasive suppurative infections, with a remarkable endocardium sparing. Clinically, infections caused by these streptococci are satisfactorily dealt with penicillin G and cephalosporins.

Of the available cephalosporins, cefotaxime, ceftriaxone and cefepime are considered to be superior for antimicrobial treatment of patients with streptococcal BSI [46]. Finally, it is very important to highlight the importance of associating surgical excision or drainage to antimicrobial chemotherapy in order to achieve a full or near full clinical recovery.

Keywords: *S. anginosus*, *S. milleri*, brain, lung, liver, spleen, abscess.

SUMMARY

The *Streptococcus anginosus* group is widely recognized for its ability to cause invasive pyogenic infections. There are very few reports of disseminated infections sustained by members of this streptococcal group. We report a case of a highly disseminated infection and analyse previous reports from the literature. Disseminated pyogenic infection has been defined as an infection affecting two or more of the following organs/systems: central nervous system, lung, liver and spleen. We performed a PubMed search using the terms: "*S. milleri*", "*S. anginosus*", "brain abscess", "pulmonary abscess", "hepatic abscess" and "spleen abscess". We reviewed 12 case reports including that presented in this paper.

Underlying conditions such as dental infections, malignancy, gastrointestinal and respiratory tract disease accounted for 42% of cases. No definite endocarditis was encountered, even though positive blood cultures were found in 67% of patients. Concomitant brain-liver, brain-lung and brain-spleen involvement occurred in 50%, 42% and 8% of cases respectively. Ninety-one percent (91%) of patients were treated with β-lactams, and surgical procedures were performed in 67% of patients.

Infections caused by *S. anginosus* group members are satisfactorily treated with penicillin G and cephalosporins. It is very important to associate surgery to antimicrobial chemotherapy in order to achieve a full or near-full clinical recovery.

RIASSUNTO

Il gruppo Streptococcus anginosus *è ampiamente conosciuto per la sua capacità di causare infezioni piogeniche invasive. In letteratura è riportato un numero esiguo di infezioni disseminate sostenute da questo gruppo di streptococchi. Descriviamo qui il caso di una grave infezione disseminata e forniamo un'analisi della letteratura relativa alle infezioni sostenute dai membri del gruppo* S. anginosus *con coinvolgimento di due o più dei seguenti organi/sistemi: sistema nervoso centrale (SNC), polmoni, fegato e milza. Abbiamo eseguito una ricerca su PubMed utilizzando i seguenti termini: "S. milleri", "S. anginosus", "brain abscess", "pulmonary abscess", "hepatic abscess", "spleen abscess". Abbiamo analizzato 12 casi, incluso quello presentato in questo articolo.*
Condizioni predisponenti come infezioni odontogene, neoplasie, malattie del tratto gastroenterico e delle vie respiratorie si sono osservate nel 42% dei casi. Non è stata mai dimostrata un'endocardite certa, anche se nel 67% dei pazienti sono state documentate emocolture positive. Il coinvolgimento concomitante del SNC e del fegato, del SNC e dei polmoni, del SNC e della milza si è verificato nel 50%, nel 42% e nell' 8% dei casi, rispettivamente. Il 91% dei pazienti è stato trattato con antibiotici β-lattamici e nel 67% dei pazienti è stata eseguita anche una procedura chirurgica.
Le infezioni causate dai membri del gruppo S. anginosus *rispondono adeguatamente alla penicillina G e alle cefalosporine. La combinazione della terapia medica con quella chirurgica è fondamentale per il conseguimento della guarigione parziale o completa del paziente.*

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