CASO CLÍNICO / *CLINICAL CASE*

Síndrome de choque tóxico secundário a peritonite primária

Toxic Shock Syndrome complicating primary peritonitis

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/ Resumo

A doença invasiva a *Streptococcus* do grupo A tem sido descrita com frequência. No entanto, a peritonite primária e a síndrome de choque tóxico continuam a ser formas muito raras de apresentação de doença invasiva a *Streptococcus* do grupo A, especialmente em crianças. O diagnóstico é difícil, geralmente retrospetivo, quando causas secundárias de peritonite foram excluídas cirurgicamente e se obteve um resultado cultural positivo. A deteção de DNA bacteriano por *polymerase chain reaction* é uma técnica diagnóstica particularmente importante quando os antibióticos são iniciados antes da intervenção cirúrgica.

Apresentamos o caso de uma adolescente com peritonite primária a *Streptococcus* do grupo A e síndrome de choque tóxico, revendo as principais dificuldades no diagnóstico e tratamento desta patologia potencialmente fatal.

Palavras-chave: Streptococcus do grupo A; Peritonite primária; Síndrome do choque tóxico

/ Abstract

Although invasive infections associated with Group A **Streptococcus** *have been reported with increasing frequency, primary peritonitis and Toxic Shock Syndrome remains an exceedingly rare form of presentation of Group A Streptococcus invasive infection in children. Its diagnosis is difficult, usually retrospective, when secondary causes of peritonitis have been ruled out by surgery and a positive result has been obtained by culture. The detection of bacterial DNA by polymerase chain reaction is a particularly important diagnostic tool, especially when antibiotics are given prior to surgery.*

We present a case of an adolescent with Group A **Streptococcus** *primary peritonitis and Toxic Shock Syndrome and review the main difficulties in diagnosis and treatment of this serious condition.*

Keywords: *Group A* **Streptococcus***; Primary peritonitis; Toxic Shock Syndrome*

/ Introduction

Group A *Streptococcus* (GAS) causes a broad range of infections with varying clinical severity. The most common GAS diseases are pharyngitis and skin infections. Less commonly, GAS causes invasive disease defined by the presence of GAS at a normally sterile body site including Streptococcal toxic shock syndrome (TSS), necrotizing fasciitis, septicemia, meningitis, pneumonia, suppurative arthritis and osteomyelitis. [1][2][3][4]

Invasive infections associated with GAS were first described in the 1980s and have been reported with increasing frequency. These infections have high mortality rates (4-32%), especially if patients meet the criteria for Streptococcal TSS (table 1). [3][5][6] It is characterized by shock and multiorgan failure resulting from capillary leak and tissue damage due to release of inflammatory cytokines induced by toxin-producing GAS strains. Streptococcal TSS complicates approximately one third of invasive GAS disease cases. [7]

Risk factors to invasive GAS disease include age (highest incidence in the elderly, followed by young children), viral infections (varicella), injecting drug use, alcoholism, immunosuppression, diabetes, malignancy, and recent childbirth. [3][4][6]

Peritonitis is defined as an inflammation of the peritoneum and can be primary, secondary or catheter-related. Primary bacterial peritonitis occurs in the absence of an evident intra-abdominal source of infection. [8][9][10] Children with medical conditions like cirrhosis, malignancy, congestive heart failure, nephrotic syndrome, systemic lupus erythematosus or immunosuppression are more susceptible, occurring infrequently in healthy children without these predisposing conditions. [8][11][12]

The most common causes of primary peritonitis in healthy children are *Streptococcus pneumoniae* and gram-negative bacteria (*Escherichia coli*, *Klebsiella pneumoniae*), although GAS peritonitis has been increasingly recognized. However, Streptococcal TSS presenting as primary peritonitis in previously healthy children remains exceedingly rare. [8][9][12]

TABLE 1 – CASE DEFINITION OF STREPTOCOCCAL TOXIC SHOCK SYNDROME

CLINICAL CRITERIA
Hypotension plus two or more of the following:
• Renal impairment;
• Coagulopathy;
• Liver involvement;
• Acute respiratory distress syndrome;
• Generalized erythematous macular rash;
• Soft tissue necrosis.
DEFINITIVE CASE
Clinical criteria plus isolation of Group A *Streptococcus* from a normally sterile site.
PROBABLE CASE
Clinical criteria plus isolation of Group A *Streptococcus* from a nonsterile site.

Antibiotic therapy is the mainstay of treatment in primary peritonitis. A broad-spectrum antibiotic, such as third generation cephalosporin, is usually started empirically and changed according to later culture results. It remains unclear whether surgical exploration and lavage of the abdominal cavity improves the prognosis; however it must be considered as it reduces intra-abdominal bacterial load. [10] The management of streptococcal TSS includes a combination of supportive therapy for septic shock and associated complications, surgical debridement of infection, antimicrobial therapy (penicillin/clindamycin) and administration of intravenous immune globulin. [6][10]

We present a case of an adolescent with GAS primary peritonitis and TSS and review the main difficulties in diagnosis and treatment of this serious and potentially fatal disease.

/ Case presentation

A 14-year-old girl presented to the emergency room with a 3-day history of fever and generalized myalgia, lower quadrants abdominal pain and nonbloody diarrhea. She had unremarkable medical history and denied any sexual activity. On physical examination she appeared unwell, with severe pain, sunken eyes, dry mucous membranes, increased abdominal wall rigidity with guarding and rebound tenderness most evident in the lower quadrants. Laboratory testing on admission revealed leukocytosis (15.500/uL) with neutrophilia (14.700/uL; 94,8%), c-reactive protein (CRP) 30 mg/dL, creatinine 1,94 mg/dL, urea 65 mg/dL with normal electrolytes.

A provisional diagnosis of acute gastroenteritis associated with colitis was stated. She was admitted and antibiotic treatment with ampicillin, gentamicin and metronidazole was initiated. Six hours after admission the patient condition deteriorated rapidly with worsening abdominal pain, vomiting, tachycardia and hypotension (blood pressure 74/48 mmHg). Blood tests were repeated and are summarized in table 2. Abdominal ultrasound failed to visualize the appendix, but did demonstrate free fluid between intestinal loops and dilatation of bowel loops. The patient received emergent intravenous fluid resuscitation with 20 mL/Kg of normal saline solution (0,9% NaCl) and 2 units of fresh frozen plasma for prolonged clotting times. Explorative laparoscopy showed extensive fibrinous purulent peritonitis and moderately inflamed uterus and fallopian tubes; the appendix and ovaries showed no signs of inflammation. Lavage of the abdominal cavity was performed, peritoneal fluid cultures were obtained and the antibiotic regimen switched to cefoxitin, doxycycline and metronidazole due to the suspicion of pelvic inflammatory disease. Cytochemical analysis of peritoneal fluid was not performed. Subsequent laboratory blood tests revealed normocytic normochromic anemia, thrombocytopenia and liver dysfunction (table 2). Persistently elevated levels of inflammatory markers prompt the addition of gentamicin to the antibiotic regimen. The patient showed gradual clinical recovery with resolution of fever and hemodynamic improvement from day 2 of admission. Abdominal pain, nausea and vomit lasted several days, with complete recovery by day 27 of admission. Blood and stool cultures, collected before antibiotic therapy, vaginal cultures and peritoneal fluid, collected during surgery after initiation of antibiotics, were all negative. She completed 14 days of cefoxitin, doxycycline and metronidazole and 7 days of gentamicin.

Peritoneal fluid collected during surgery was tested for bacterial DNA using a polymerase chain reaction (PCR) method and was positive for DNA of *Streptococcus pyogenes* establishing the diagnosis of GAS primary peritonitis.

/ Discussion

The mechanism of primary GAS peritonitis is not completely understood, however an ascending route of infection in the female genital tract, hematogenous spread from remote source in respiratory tract or skin and translocation from gastrointestinal tract has been suggested. [9][12][13] In our patient, without sexual activity, the ascending route of infection would be unlikely. However, laparoscopic evidence of moderately inflamed uterus and fallopian tubes could suggest an ascending route of infection. Unfortunately, vaginal cultures were collected after initiation of antibiotics, so a proof of the source of infection was not possible.

The clinical presentation of our patient was similar to the published cases of primary GAS peritonitis: severe abdominal pain, fever and flu-like symptoms such as myalgias. Imaging may be useful in the management of primary peritonitis, however surgical assessment is frequently necessary. [12][14] In our patient, ultrasound findings were unhelpful in establishing whether the clinical presentation was a result of a surgical cause (the appendix was not visualized) so an exploratory laparoscopy was necessary.

During hospital stay, the patient condition deteriorated rapidly presenting with abdominal septic shock of unknown etiology. Since all cultures were negative, the diagnosis of GAS TSS was established retrospectively by PCR of peritoneal fluid. The use of 16S ribosomal RNA gene PCR allows detection of live or dead bacteria by nucleotide sequence amplification and analysis, especially in patients with a high clinical suspicion of infection and negative cultures or undergoing antibiotic therapy [15][16]. Despite the wide implementation of 16S rRNA gene PCR, there are few evidence-based studies addressing its diagnostic impact in invasive GAS disease; sensitivities of 84% for 16S rRNA gene PCR and 77.3% for culture have been reported. [17]

Because it is extremely infrequent, there are no standardized recommendations for management of GAS primary peritonitis. [10][12] Regarding antibiotic treatment, because a secondary cause of peritonitis is initially suspected, empirical therapy with broad-spectrum antibiotics covering intestinal flora are started initially,

TABLE 2 – LABORATORY RESULTS			
RESULTS	**12H ADMISSION**	**DAY 5 ADMISSION**	**REFERENCE VALUES**
Hemoglobin (g/dL)	13,7	9,9	11,7-15,3
Leukocytes (/ML)	6.600	11.600	4.000-11.000
Neutrophils (/ML)	6.200 (94%)	10.200 (89%)	1.800-6.900
Lymphocytes (/ML)	200 (3,2%)	1000 (0,1%)	1.200-3.300
Platelets (/ML)	181.000	119.000	150.000-400.000
CRP (mg/dL)	41,5	32,1	<0,3
Prothrombin time	33,6	27,1	10-14
INR	2,6	2,3	<1,2
Activated partial thromboplastin time (secs)	37	32,2	20,6-29,5
Fibrinogen (g/L)	5,6	8,5	1,8-3,5
D-dimers (Mg/L)	3951	9557	<500
Urea (mg/dL)	85	45	19,3-44,9
Creatinine (mg/dL)	1,84	0,67	0,60-1,00
eGFR (ml/min/1,73m^2)	40	128	>90
Aspartate aminotransferase (AST) (U/L)		120	0-26
Alanine aminotransferase (ALT) (U/L)		90	19-44
Alkaline phosphatase (U/L)		321	103-283
Amilase (U/L)		350	<106
Serum proteins (g/L)		5,51	6,4-8,2
Albumin (g/L)		1,92	3,8-5,6
Human immunodeficiency virus type 1 and 2 antibody	Negative		
Hepatitis C antibody	Negative		
Hepatitis B surface antigen	Negative		
VDRL	Negative		
Blood gas analysis			
pH	7,305		7,37-7,45
pCO_2	36,1 mmHg		35,0-46,0
$HCO3^-$	17,6 mmol/L		21,0-26,0
Base Excess	-8 mmol/L		
Lactate	4,480 mmol/L		<1,800

as in our case. The late identification of GAS in our patient compromised institution of directed antimicrobial therapy.

To summarize, in a young, previously healthy girl who presents with acute abdominal pain but lack imagiologic signs of secondary peritonitis, GAS primary peritonitis should be considered. These patients require prompt antibiotic therapy and, if shock is present, aggressive resuscitation therapy. Surgery may be required if diagnostic imaging findings are nonspecific and secondary peritonitis cannot be excluded, for fluid sample and peritoneal lavage. [9]

This case report also emphasizes the benefit of bacterial PCR in detecting the causative agent of a primary peritonitis, essentially when antibiotics are given prior to surgery.

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