
Caso Clínico / Clinical Case

***STREPTOCOCCUS GALLOCYTICUS* BACTERAEMIA ASSOCIATED WITH COLONIC ADENOMATOUS POLYPS**

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Resumo

A bacteriémia por *Streptococcus gallolyticus* associa-se frequentemente ao carcinoma colorrectal, tornando obrigatória a colonoscopia nestas situações. A endocardite bacteriana e a artrite séptica são também comuns neste tipo de bacteriémias. Tem sido levantada a hipótese das bactérias intestinais poderem ter um papel promotor de hiperproliferação celular aberrante em lesões cólicas pré-neoplásicas, aparentemente devido a processos inflamatórios crónicos e produção de metabolitos carcinogénicos. Os autores apresentam o caso dum doente com vários pólipos adenomatosos tubulares do cólon direito, em dois dos quais se demonstrou uma área de displasia de alto grau adjacente a zona de colite infecciosa bacteriana, associados a quadro clínico de infeção sistémica por *Streptococcus gallolyticus* e artrite do tornozelo.

Summary

Bacteraemia due to *Streptococcus gallolyticus* is frequently associated with colorectal carcinoma, making evaluation of the gastrointestinal tract by colonoscopy obligatory in such cases. Bacterial endocarditis and purulent arthritis are also common in patients with these bacteraemias. Intestinal bacteria could behave as promoters of aberrant hyperproliferative behaviour in preneoplastic colorectal lesions, apparently due to chronic inflammatory processes and production of carcinogenic metabolites. The authors treated a patient with several tubular adenomatous polyps of the right colon, two of which showed areas of high-grade dysplasia adjacent to areas of infectious bacterial colitis associated with *Streptococcus gallolyticus* bacteraemia and unilateral ankle arthritis.

GE - J Port Gastroenterol 2006, 13: 152-156

INTRODUCTION

The aetiology of colon cancer can be related to environmental and hereditary factors (1). Bacteria have been linked to cancer by two mechanisms: chronic inflammation and production of carcinogenic metabolites (2). Intestinal microflora has been reported to have an action on the pathogenesis of colon cancer (3). For some authors it appears to act as a promoter of aberrant hyperproliferative behaviour in preneoplastic lesions (4). It would be of interest to substantiate any relationship between *Streptococcus gallolyticus* (formerly known as *Streptococcus bovis* 1) (5) colonic carriage, colonic polyps and particularly the type of polyp and its malignant potential. Burns (6) demonstrated that highly pre-malignant polyps were found to be more often associated with *Streptococcus gallolyticus* carriage than were benign polyps. The frequency of involvement of *Streptococcus gallolyticus* bacteraemia in colorectal neoplasia is, however, the subject of controversy, due to its association with both benign (diverticulosis, inflammatory bowel disease, cecal volvulus, perirectal abscess,

hemorrhoids, benign polyps) and malignant disease of the colon (6,7,8).

Enterococci are the predominant *Streptococci* isolated from human feces, but *Streptococcus gallolyticus* has also been found in the faecal flora of 10 to 16% of healthy human subjects (6,9). In an interesting study by Leport (10) of 77 infections with group D *Streptococcus endocarditis*, colonic polyps were significantly more frequent in the *Streptococcus gallolyticus* group (67%) than in the *Enterococcus* group (21%). In this study, the frequency of colonic carcinoma was also significantly higher in patients found to have *Streptococcus gallolyticus* endocarditis (18%) than in patients with *Enterococcus* endocarditis (2%). Isolation of *Streptococcus gallolyticus* in blood cultures is diagnostically significant, because this bacteria is a normal inhabitant of the gastrointestinal tract, and bacteraemia and endocarditis due to these bacteria are often associated with colorectal neoplasia (11,12,13,14). A full evaluation of the gastrointestinal tract in patients with *Streptococcus gallolyticus* bacteraemia, with or without endocarditis, is mandatory, due to high frequency of isolation of

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Streptococcus gallolyticus in the blood of patients with various gastrointestinal diseases (6,7,8). Pyogenic arthritis as a complication of colonic neoplasia was also referred to by some authors (15,16,17).

Recently it was reported that patients with colorectal cancer have increased faecal carriage of *Streptococcus gallolyticus* (56%) compared to normal individuals and patients with benign diseases of the colon, such as colonic diverticulosis, inflammatory bowel disease, cecal volvulus, perirectal abscess and hemorrhoids (10-23%) (6,7,8). The lower percentages of faecal carriage of *Streptococcus gallolyticus* found by Burns (6) were attributed by the author to the different methodology of the study, but even so, a statistical significant, progressively higher percentage of faecal carriage of *Streptococcus gallolyticus* was demonstrated between normal individuals and patients with tubular adenomas, tubulovillous adenomas, villous adenomas and patients with colorectal cancer. These results raise the question of whether it is the malignant milieu of the colon that promotes the growth of *Streptococcus gallolyticus* or if *Streptococcus gallolyticus* contributes in some way to the malignant milieu. (6).

In addition to colorectal cancer, there have been a few reports of *Streptococcus gallolyticus* bacteraemia associated with colonic adenoma (6, 18). The authors treated a patient with several tubular adenomatous polyps of the right colon, two with areas of superficial high-grade dysplasia, one of which was ulcerated. However, surgical sampling did not reveal high-grade dysplasia, rather it showed only several tubular adenomas with low-grade dysplasia, together with adjacent apparent features of infectious colitis on the ulcerated polyp. No malignant tissue was detected, and the patient is well and shows no signs of malignant evolution one year after right hemicolectomy, although we recently found four other adenomatous polyps that probably went undetected in the previous colonoscopy. Two of these were tubulovillous adenomas with low-grade dysplasia and two were tubular adenomas, one with high-grade dysplasia occupying 5% of the glandular area.

CLINICAL REPORT

A 55 year old Caucasian man was admitted to our Unit in October 2004 complaining of a fever (37.8-38.5° C) almost every evening, of three weeks duration, along with nocturnal diaphoresis and intermittent arthralgia of the right ankle. He denied any other symptoms. He reported frequent consumption of cottage cheese and that he had been to Tunisia the month before. He appeared well nourished and somewhat pale.

Temperature was 38.2°C, blood pressure 130/70 mm Hg, heart rate 100 beats p/min. Thoracic and abdominal examinations were normal. There were no signs of anaemia. Painful swelling of the right ankle was apparent, although without other signs of inflammation and infection. Digital rectal touch was normal.

LAB tests revealed: slight normocytic, normochromic anaemia (Hgb 10.8 g/dL), no leucocytosis, normal platelets, ESR 79 mm/1st hour, normal coagulation tests; normal SMA-12 biochemical profile; normal serum immunoglobulins; negative ANA, DNA and Coombs tests; slightly elevated C3, C4 and haptoglobin levels. Serology for HAV, HBV, HCV, HIV, CMV, EBV, *Herpes virus*, *Yersinia*, *Brucella*, *Borrelia* and *C. burnetti* were all negative; CEA and CA 19.9 levels were normal. Meanwhile, x-ray of the ankle and CT scans of the thorax and abdomen were normal. No endocarditic vegetations were detected on echocardiogram. A complete colonoscopy revealed several sessile and pediculated polyps on the right colon of varying sizes, one morulated polyp at 70 cm (8 mm), one sessile polyp at 80 cm (1,5 cm) and two contiguous sessile polyps at 100 cm (3 cm) (Figure 1). Biopsies of the polyps showed features of tubular adenomas with low-grade dysplasia on the polyp at 70 cm and high-grade dysplasia on the polyps at 80 and 100 cm. After this examination we decided to begin empirical antibiotic therapy with gentamicin and ceftriaxone. The patient became afebrile after the second day of therapy and the arthritis was promptly resolved. Seven days after the colonoscopy, five blood cultures taken the day of admission were all positive for *Streptococcus gallolyticus*, sensitive to penicillin G, ampicillin, cefotaxime, erythromycin and clindamycin. Nevertheless, we decided to continue the previously instituted empiric therapy for a complete course of 15 days, due to the good response to therapy. Two consulting gastroenterologists decided on definitive surgical

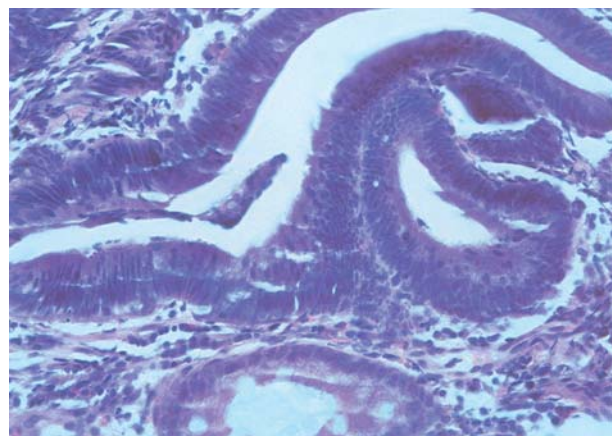


Figura 1 - HEx10: Colon biopsy: tubular adenoma with high-grade dysplasia.

treatment. This decision was based on the size and histopathology of the biggest polyp and its unresectability, the friability of the right hemicolon, and also because it was associated with bacteraemia in five blood cultures, due to the risk of recurrent bacteraemia and possible complications, such as endocarditis. A right hemicolectomy was performed, the surgical specimen revealing a greater number of polyps than were seen on the colonoscopy - both sessile and pediculated polyps at various distances from the distal border: at 5 cm (sessile polyp 4x2x1.5 cm), 6.5 cm (depression area with effacement of the mucosal folds 3x2x0.9 cm) (area of previous biopsy?), 11 cm (two pediculated polyps: 2x1 cm and 2.6x0.5 cm); 14.5 cm (sessile polyp 0.5x0.3 cm), 16 cm (sessile polyp 4.5x3x1 cm), 21.5 cm (sessile polyp 0.3 cm) and 29 cm (sessile polyp 0.9x0.5 cm). On microscopic view the polyps were all tubular adenomas with low-grade dysplasia (Figure 2). No areas of high-grade dysplasia were found in the surgical sample. The biggest of the polyps was ulcerated and had intense transmural neutrophil inflammatory infiltrate (Figure 3) with phlegmonous areas, abscesses and tissue necrosis. The epithelium of the polyps showed areas of accentuated crypt reduction and foci with crypt abscesses (Figure 4), due to infectious colitis, and ischemic colitis. Acute perintestinal lymphadenitis with sinus histiocytosis was conspicuous, but no neoplastic tissue was identified. These histopathological features suggested a continuing local infectious process despite the apparently good response to antibiotic therapy. No history of prior colon disease was elicited and nor was there any family history of colonic polyposis or colorectal cancer. One year after surgery the patient was doing well, but a follow up colonoscopy done at that time showed four other pediculated polyps, which in retrospect we believe, based on their size, had probably been missed on the previous colonoscopy due to less than optimal bowel cleansing.

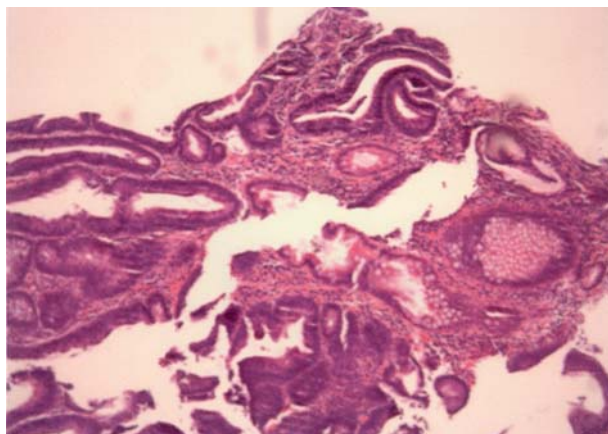


Figure 2 - HEx5: Surgical sample of right colon: tubular adenomas with low-grade dysplasia.

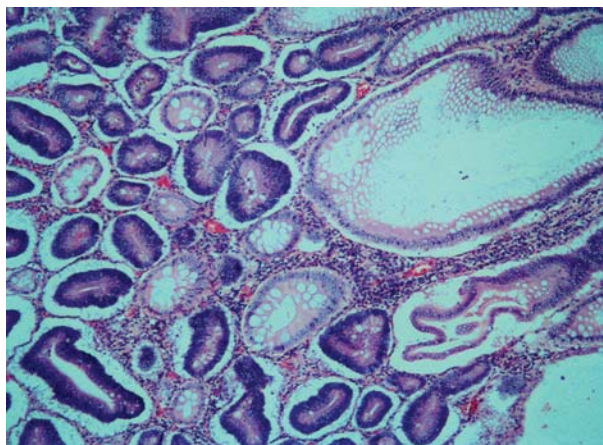


Figure 3 - HEx10: Surgical sample of right colon: tubular adenoma with associated inflammatory infiltrate.

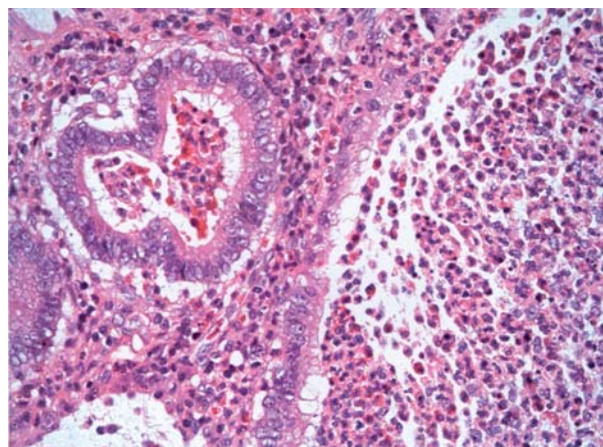


Figure 4 - HEx40: Surgical sample of right colon: tubular adenoma with intense granulocytic inflammatory infiltrate and with crypt abscess.

These were located at 30 cm (10 mm) on the sigmoid colon, at 60 cm (1x0.5 cm), at 62 cm (0.8x0.5 cm) and at 65 cm (2mm) on the transverse colon. All the polyps were removed by colonoscopic polypectomy. The first polyp was a tubular adenoma with low-grade dysplasia, the second and the fourth polyps were tubulovillous adenomas with low-grade dysplasia, but the third polyp was a tubular adenoma with focal high-grade dysplasia occupying 5% of the glandular area. The basal areas of all the polyps did not reveal dysplasia and neoplastic tissue. A follow up colonoscopy will be done in one year's time and, if normal, again within two to three years. If it continues to be normal, future monitoring will be done with colonoscopies every 3 to 5 years.

DISCUSSION

Due to the common association between *Streptococcus gallolyticus* bacteraemia and colorectal cancer and

tubulovillous and villous adenomas, even in patients without previous bowel symptoms, it is recommended that these patients undergo full colonoscopy to screen for colorectal cancer (12,16,17). Changes in local conditions and disruption of capillary channels at the site of co-lorectal neoplasias allow *Streptococcus gallolyticus* to proliferate and gain entry into the blood stream.

Cells that line the mucosal surface of the bowel form a major mechanical barrier that separates the host's internal milieu from the external environment and function as an integral component of the mucosal immune system. There is intercellular functioning and an amplifying communication network through delivered signals induced by cytokines produced by a number of different cells at the level of bowel mucosa. These cytokines deliver signals that influence the activation, growth, differentiation, or migration of the target cells upon which they act. Individual cells can produce multiple cytokines. Microbial entry is important in the activation of this cytokine signalling network (19).

Since the cytokines expressed in response to bacterial invasion or to other pro-inflammatory agonists have a well documented role in chemotaxis and activation of inflammatory cells, colon epithelial cells appear to be programmed to provide a set of signals for activation of the mucosal inflammatory response in the earliest phases after microbial invasion. Some cytokines and chemokines activate a spectrum of pro-inflammatory effects (IL-1, IL-8, TNF- α , GM-CSF, monocyte chemoattractant protein-1), whereas others downregulate inflammatory responses (IL-10, TGF β 1). Invasion of the intestinal mucosa by pathogenic bacteria leads to a marked acute mucosal inflammatory response, induced by the cytokine system network, which is characterized histologically by infiltration with neutrophils and macrophages/monocytes (19).

The adherence of *Streptococcus gallolyticus* to intestinal epithelial cells seems to be the initial process in colonization and subsequent infection of the host. The adhesion of several opportunistic bacteria to host tissue, mediated through binding to various human cell surfaces or extracellular matrix components (fibronectin, collagen and laminin) is correlated with pathogenicity and, in the case of *Streptococcus gallolyticus*, the relationship between bacteraemia/endocarditis and carcinoma of the colon suggests the existence of *Streptococcus gallolyticus* adhesins which allow colonization of both colonic and vascular tissues (4).

Bacterial adherence to various human cells induces synthesis of pro-inflammatory cytokines and chemokines, and promotes the upregulation of adhesion molecules by engaging bacterial surface adhesins of the moduline class (20). The ability of *Streptococcus gallolyticus* to

adhere to human tumour cells has not been demonstrated. However, the close relationship between *Streptococcus gallolyticus* bacteraemia and endocarditis and carcinoma suggests the existence of such a mechanism involving the reaction of bacterial adhesins with tumour cell surface receptors (21). In addition, cytokines also appear to promote and enhance bacterial adherence to various cells (22). Recent data show that TNF- α provides a microenvironment conducive to the proliferation of anaerobic bacteria, including *Streptococcus gallolyticus*, and that IL-8 secretion by colon epithelial cells from different sites is enhanced in various inflammatory diseases. Thus, the ability of *Streptococcus gallolyticus* to adhere to and stimulate human cells may contribute to the pathogenicity of the bacteria (22).

It was reported that the local action of cytokines or of chemical mediators able to promote vasodilatation and enhancement of capillary permeability may support bacterial entry at the tumour site and increase bacterial adherence to various cells (23). Some authors refer to the potential involvement of *Streptococcus gallolyticus* in intestinal carcinogenesis. Ellmerich (4), in a very interesting experimental study in rats, demonstrated that *Streptococcus gallolyticus* or its antigens promoted progression of pre-neoplastic lesions through increased formation of hyperproliferative aberrant colonic crypts, enhanced expression of proliferative markers and increased production of IL-8 in the colonic mucosa. Bacterial cell wall proteins were found to be more potent inducers of neoplastic transformation than the intact bacteria. On the other hand, these abnormalities were only demonstrated when pre-neoplastic lesions were already present and not in normal mucosa (4).

Production of inflammatory cytokines, such as TNF- α , IL-1 β and IL-6, and the chemokine IL-8, contribute to the normal host defence mechanisms (24), leading to the formation of nitric oxide and free radicals, such as superoxide, peroxynitrites and hydroxyl radicals, as well as alkylperoxy radicals (25). Owing to their potent mutagenicity, all these molecular species can contribute to neoplastic processes by modifying cellular DNA. In addition, the production of angiogenic factors, such as IL-8 triggered by *Streptococcus gallolyticus* antigens, in the colonic mucosa may also favour the progression of colon carcinogenesis (26,27).

Contrary to the more commonly reported association between *Streptococcus gallolyticus* bacteraemia and colorectal cancer, a link to pre-neoplastic adenomatous polyps was rarely reported (4,6,18). Although we cannot assume a cause and effect relationship in the case of our patient, the clinical report includes several commonly assumed criteria that support the hypothesised relationship between colorectal *Streptococcus gallolyticus*

infection and the progressive development of malignant disease in pre-neoplastic adenomatous polyps. Pyogenic arthritis in a patient with colonic neoplasia is also described by several authors (14,15,16). In our case the arthritis was probably related to *Streptococcus gallolyticus* bacteraemia but without the development of pyogenic arthritis, and it behaved as a reactive-type arthritis.

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