ASSOCIATION OF UTERINE LEIOMYOMA AND CHAGAS’ DISEASE

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INTRODUCTION

The association between Chagas’ disease and neoplasias has been a focus of studies and a point of controversy.1–6 It has been associated with a greater frequency of malignant neoplasias in Chagas’ disease patients than in non-Chagas’ disease patients; in a comparison of the tumor sites, a significantly greater frequency of esophagus cancer and uterine cervix in the Chagas group was observed.3 A revision of necropsies showed that there was greater frequency of carcinomas of the esophagus among Chagas’ disease patients with megaesophagus compared with non-Chagas’ disease patients. Nonetheless, given that the frequency of this neoplasia was similar among Chagas’ disease patients with megaeosophagus and non-Chagas’ disease patients, the authors emphasized that the association appeared to be with the megaesophagus and not just with the Chagas infection.4

Also, the association of chagasic megacolon and colon cancer have been reported in literature.7 Nevertheless, others did not find such association.8 In an experimental study, rats with induced megacolon that were submitted to a carcinogenic substance had a significantly lower frequency of colon cancer compared with controls.9 Adad and others6 described a case involving an association of neoplasia of the smooth musculature of the esophagus with Chagas’ disease. Taken together, these reports led us to questioning the frequency of uterine leiomyoma in Chagas’ disease patients.

Uterine leiomyoma is a benign neoplasia of the smooth musculature, with an incidence of about 20% among women at the menacme.10 At autopsy, this percentage rises to 50%.11 Its etiopathogenesis is related to genetic and hormonal factors.10 These tumors are found most frequently in Black women between the ages of 40 and 49 years who are pauciparous (three or fewer previous pregnancies) and have a family history of this neoplasia.12 Other factors such as high socioeconomic and educational levels and high levels of stress also appear to be related to greater frequency of this uterine neoplasm.13–16 Multiparity and smoking are considered as factors protecting against the development of leiomyoma.15–19

Because some literature data have suggested a relationship between Chagas infection and neoplasias and studies now exist regarding Chagas’ disease and neoplasia of the smooth uterine musculature, we aimed to study prospectively the frequency of Chagas’ disease in patients undergoing surgery for uterine leiomyoma.

MATERIALS AND METHODS

Patients selected. The study group consisted of women older than 35 years who underwent surgery between January 1998 and July 2000 because of a clinical and ultrasonographic diagnosis of leiomyoma or because of grade II (cervix protruding outside the hymen) or III (uterus fully outside the hymen) uterine prolapse whose anatomicopathological examination demonstrated the presence of leiomyoma. The indications for abdominal hysterectomy or leiomymectomy were uterine volume greater than 300 cm³ or the presence of transvaginal hemorrhage with failure of the clinical treatment. The indication for vaginal hysterectomy was the association with uterine prolapse. This research was approved by the Committee for Ethics in Research of the Faculty of Medicine of “Triângulo Mineiro” (FMTM).

Serological tests. The serology for Chagas’ disease was performed on the blood collected for the preoperative examinations. The diagnosis of Chagas infection was based on positivity to at least two of the following three reactions: enzyme-linked immunosorbent assay (ELISA; kit of Salk), passive hemagglutination Sion (Hemacruzi, Biolab), and indirect immunoﬂuorescence tests (Immunocruzi [lyophilized] and conjugate [anti-human globulin with fluorescein]), Biolab for Trypanosoma cruzi). In the control group, the women presented with negatives tests.

Statistical analysis. The study was case controlled, matching for age, skin color, and parity. The control group was composed of patients undergoing either surgery for benign breast alterations or corrections of pelvic organ prolapse or hysterectomies for benign alterations without signs, symptoms, imaging (ultrasonography or video laparoscopy), or anatomicopathological examination showing uterine leiomyoma. The data were analyzed using Fisher’s exact test; the level of significance set at less than 0.05.

RESULTS

During this period, 118 women underwent surgery with a diagnosis of leiomyoma from anatomicopathological exami-
nation. Of this group, 111 (94.1%) underwent total abdominal hysterectomy and 7 (5.9%) vaginal hysterectomy because of an association with grade II or III uterine prolapse. In the control group (n = 118), the reasons for surgery were as follows: correction of pelvic organ prolapse (enterocele, rectocele, and vaginal vault prolapse) with the exception of uterine prolapse (n = 36 [30.5%]); tubal sterilization by video laparoscopy (n = 33 [27.9%]); exploratory laparotomy or video laparoscopy for a benign ovarian cyst (n = 24 [20.3%]); benign breast nodule (n = 9 [7.7%]); vaginal hysterectomy for grade II or III uterine prolapse (n = 8 [6.8%]); extirpation of Bartholin’s gland (n = 8 [6.8%]). Histological analysis of leiomyoma was performed routinely (one fragment for each squared centimeter of leiomyoma). In all cases, the leiomyomas had a common aspect. Histopathological evidence for chronic Chagas’ disease was not observed.

The average age of patients with uterine leiomyoma was 51.8 ± 11.1 years and for the control group, 49.5 ± 10.3 years. The distribution for each group with regard to skin color and parity was as follows: 43 (36.5%) pauciparous Whites, 20 (16.9%) multiparous Whites, 25 (21.2%) pauciparous non-Whites, and 30 (25.4%) multiparous non-Whites.

Table 1 shows the distribution of all patients according to serology. A greater frequency of Chagas’ disease can be observed among women with uterine leiomyoma. Among patients with serology positive for Chagas’ disease, 62.7% had uterine leiomyoma versus 46.5% of the control group (P < 0.05).

Table 2 and 3 show the distribution of White and non-White women with uterine leiomyoma and the controls according to the parity and serology for Chagas’ disease. Multiparous White women with uterine leiomyoma presented more frequently with serology positive for Chagas’ disease compared with the control group.

### DISCUSSION

Chagas’ disease is endemic in some regions of Brazil and is considered to be a public health problem because of their complications. This disease predominantly affects inhabitants of rural areas and generally those of low socioeconomic and cultural level, independent of race, sex, or color. The FMTM Teaching Hospital is a tertiary referral hospital with free public attendance. The individuals served there are normally of low socioeconomic and cultural level; the majority originate from the Triângulo Mineiro (western extremity of the State of Minas Gerais), situated in central Brazil, a region where Chagas’ disease is endemic. Because of the combat programs, vectorial transmission in this region has in practice been extinct for 30 years. For this reason, we selected for this study only those women older than 35 years. Currently, we have no data related to the background rate of seropositivity in general population in the area of the study.

The majority of individuals become infected while they were still young, and the infection causes cell destruction throughout their lives. Because of this action, the antineoplastic effect of an extract of T. cruzi has been described. However, others have not confirmed these results, especially when the extract of T. cruzi was used in mouse. One possible antitumoral effect could be explained by the release of many endocellular antigens after the destruction of parasitic neoplastic cells, which stimulates an increase in the immune response. Nonetheless, this possible antitumoral effect weighs against our findings.

Our results demonstrated that 21.6% of the patients undergoing gynecological surgeries had positive serology for Chagas’ disease. In the group with leiomyoma, the percentage of Chagas cases was greater: 27.1% versus 16.1% for the controls. Considering that the population studied was from a low socioeconomic and cultural level, the results suggest an association between Chagas’ disease and uterine leiomyoma.

Uterine leiomyoma is considered to be a hormone-dependent tumor because of its greater frequency among multiparous women and at menopause as a result of its increase in volume during pregnancy and its regression postpartum and at menopause. Black and pauciparous women are those who present with greatest frequency. Nevertheless, our findings show a greater frequency of uterine leiomyoma among multiparous White women who are serologically positive for Chagas’ disease compared with the controls. This result reinforces the finding of an association between Chagas’ disease and uterine leiomyoma.

This association is difficult to explain. Because this was a case-controlled study, epidemiological variables such as skin color, age, and parity were matched and possibly excluded. To explain this finding, a few hypotheses arise. Could the parasitism of the uterine muscle fiber increase the incidence...
of myoma? Parasitism by *T. cruzi* has already been demonstrated in the murine uterus. In their 2000 report, Concetti and others described a case of Chagas’ disease in the uterine cervix of a woman with AIDS; the patient died 5 months after Chagas cardiopathy was diagnosed.26

Cases of esophageal carcinoma in congenital chagasic megaeosophagus and after Merendino’s surgery have been described.27,28 In one study of 600 patients with megaeosophagus undergoing endoscopy, 0.8% of patients had esophageal carcinoma.29 Endoscopy as a routine procedure in the megaeosophagus is proposed as a result of this morbidity.27,29 One study demonstrated that p53 overexpression and mutational change are early events in patients with achalasia.30 In Chagas megaeosophagus, there is an inflammatory process in the diverse layers, and outbreaks of myositis are commonly encountered, as are hypertrophy or hyperplasia of the muscle fibers.31,32 This inflammation process appears to be associated with alterations of the p53 protein.30 If the same process occurs in the uterus, it could explain our results. Another fact is that the majority of patients who underwent surgery as a result of leiomyoma had symptoms and anatomicopathological proof of this neoplasia. It may then be possible to relate Chagas’ disease to the high rate of leiomyoma, which would cause more symptomatology.

There appears to be an increase in the frequency of neoplasias in Chagas’ disease patients as a probable consequence of the treatment. Among 16 Chagas’ disease patients with cardiac transplantation, 6 (37.5%) developed neoplasia after clinical treatment (lymphoproliferative disorder, 3; Kaposi’s sarcoma, 2; squamous cell carcinoma, 1).33 The authors explained that the probable origin of these neoplasias was the result of chronic infection by an immunomodulating protozoan, immunosuppression, reactivation of the infection by *T. cruzi*, or the toxicity of the benzonidazole. Nevertheless, no scientific data correlate immunosuppressed women with the appearance of uterine leiomyoma. It was demonstrated the probable origin of these neoplasias was the result of chronic infection by an immunomodulating protozoan, immunosuppression, reactivation of the infection by *T. cruzi*, or the toxicity of the benzonidazole. Nevertheless, no scientific data correlate immunosuppressed women with the appearance of uterine leiomyoma. It was demonstrated the probable origin of these neoplasias was the result of chronic infection by an immunomodulating protozoan, immunosuppression, reactivation of the infection by *T. cruzi*, or the toxicity of the benzonidazole. Nevertheless, no scientific data correlate immunosuppressed women with the appearance of uterine leiomyoma.

To our knowledge, an association between Chagas’ disease and benign neoplasia of the smooth muscle has not been described until now. This study showed a high association between Chagas’ disease and uterine leiomyoma, although an appropriate epidemiological study with multivariate analysis is necessary to truly demonstrate a correlation between these diseases. Our findings permit us to conclude that this association does not appear to be accidental. Future investigations, such as the analysis of parasitism of the uterus and the presence of hypertrophy or hyperplasia of the myometrium, may provide support for our findings.

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