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ORIGINAL ARTICLE

Early cancer in achalasia

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SUMMARY. Esophagus achalasia is considered by many authors a preneoplasic disease and, for this reason, they propose a follow-up with endoscopies and brush cytology. For others, the possibility of cancer in achalasia is very low and the surveillance is not justified owing to its fallibility and high cost. Generally, cancer in achalasia has a late diagnosis as a consequence of megaesophagus and of many years of symptoms attributed to achalasia disease. The rate of resectability is low and 5-year survival is very poor. To define the patients who have a high risk of cancer in achalasia and to perform an early diagnosis is the challenge to improve resectability and to increase survival. The search of cancer in achalasia with endoscopies and lugol vital staining was performed in 18 out of 76 patients with achalasia. The 18 patients had enlarged esophagus and more than 10 years of evolution. Lugol negative endoscopic areas were found in 10 out of 18 patients and four out of 10 were carcinomas. Two were circular superficial erosive lesions (Tis N0 M0 and T1 N0 M0), one was an elevated multifocal lesion of less than 1 cm diameter (T2 N0 M0) and the last one was a longitudinal central ulcer of less than 1 cm diameter (T1 N0 M0). In the remaining 6 out of 10 patients the diagnosis was esophagitis. In the other 58 patients, three carcinomas were diagnosed, two advanced tumors, with endoscopy and biopsy (T3 and T4 N1) and the third one (T1 N0 M0) was a pathological finding in a resected specimen for recurrent achalasia and megaesophagus. The global prevalence was of 9.21% (7/76). The prevalence in advanced stages of achalasia was of 18.92% (7/37). The resectability rate was of 85.71%.

Conclusion: Achalasia patients with more than 20 years of evolution, enlarged esophagus with 'knees' and with marked retention must be considered to be of high risk for developing cancer. In this group, the surveillance with endoscopy and lugol vital staining or brush cytology is justified. Other common risk factors of esophageal cancer that must be considered are patients aged over 60 years who are smokers and regular consumers of alcohol.

INTRODUCTION

Achalasia is a motility disorder of the esophagus characterized by the absence of peristaltic contraction in the esophageal body and by the inability of the lower sphincter to relax completely after swallowing. This motor disorder results in stasis of the esophageal body contents, which, in turn, induces progressive enlargement and dilation of the esophagus.

Esophageal achalasia is uncommon and the etiology of this disorder is unknown in Europe and the USA.[1] It is more frequent in South America, particularly in Brazil and Argentina. It is thought to be caused by Chagas in Brazil,[2–5] but in Argentina more than 75% of the cases are idiopathic.[6]

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In advanced stages, the esophagus can become large, and kinking and 'knees' can be observed. Achalasia patients present a 3–33-fold risk of developing cancer compared to the general population.[7] Cancer would be induced by chronic mucosal irritation, which is caused by stasis esophagitis.[2,8] Several authors consider that achalasia is a preneoplastic condition[9,10] and recommend periodic surveillance with endoscopies.[11,12] On the other hand, other authors believe that cancer in achalasia incidence is very low[13] and that this kind of study is not justified for economic reasons.[14] We present our experience with seven cases of achalasia associated with squamous cell carcinoma diagnosed between 1989 and 1996. Four of these were early tumors with the appearance of erosive superficial lesions. We also try to establish, which achalasia patients present a high risk of developing cancer of the esophagus.

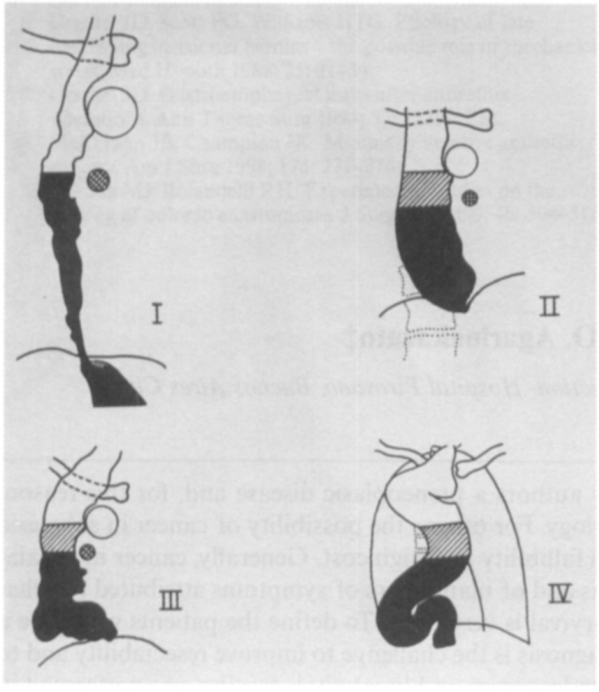

Fig. 1 Grades of achalasia.

MATERIALS AND METHODS

Between January 1989 and June 1996, 76 achalasia patients underwent surgical treatment in the Section of Esophagus Surgery, Department of Surgery, Hospital Ignacio Pirovano, Buenos Aires City. Diagnosis were based on clinical symptoms, and radiologic, endoscopic, and manometric studies. These preoperative studies diagnosed esophageal cancer in six patients.

Our series was formed by 35 females and 41 males; the mean age was 47.57 years old, with a range from 13 to 79 years. Only six out of 76 patients (7.89%) had positive serological tests for Chagas. Main symptoms were dysphagia, regurgitation and weight loss.

Radiology (barium swallow)

All patients underwent radiologic studies and were classified according to the classification used in Argentina, which was described by Resano in 1958.[15,16] Resano's classification divides achalasia patients into four grades as follows (Fig. 1):

Grade I: The esophagus presents as normal size but with marked emptying delay; the disorder is only functional; tertiary waves are observed (Fig. 2).

Grade II: The esophagus is dilated with evidence of retention but its contour is regular. It presents a fusiform appearance with a smooth tappered 'bird beak'. Absence of gastric air bublle can be observed (Fig. 2).

Grade III: Dilation increases and esophageal enlargement is observed. The esophagus overlaps the mediastinum to the right and lies on the right diaphragm forming kinks or 'knees'. There is significant esophageal retention (Fig. 3).

Grade IV: Huge dolicomegaesophagus with several 'knees' and complete atony. (Fig. 4)

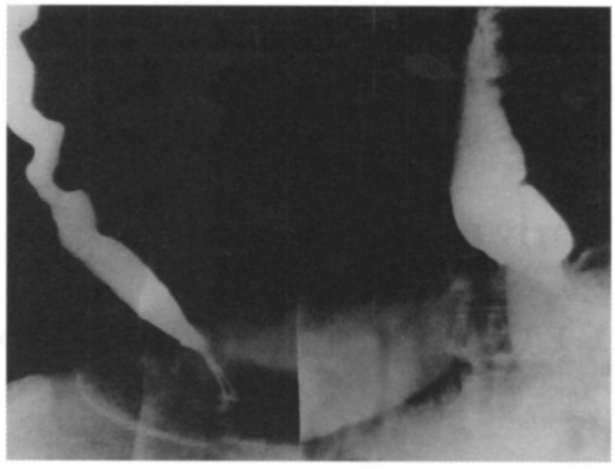

Fig. 2 Barium swallow X-ray showing grade I and II achalasia.

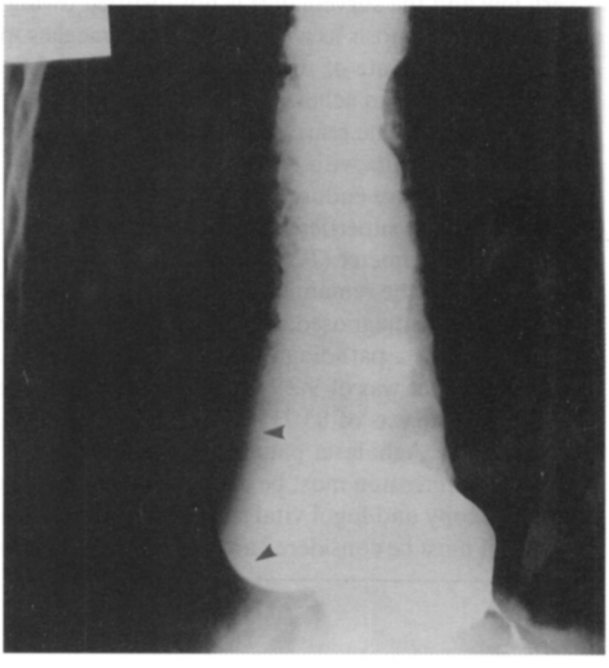

Fig. 3 In this esophagram the esophagus overlaps the mediastinum to the right diaphragm forming only one 'knee'.

Videoendoscopy

The 76 patients were evaluated with a Pentax EPM 3000 videoendoscope with EG/2900 in left lateral decubitus position. All of them underwent a 24 h fasting period and esophageal lavage with a carbonated beverage the day before. Every patient received N buthil hioscine and benzodiazepine IM as premedication. Vital staining with 2% Lugol's solution was performed in 18 patients (eight out of 10 with grade IV and 10 out of 27 with grade III) with more than 10 years of evolution. This procedure was performed

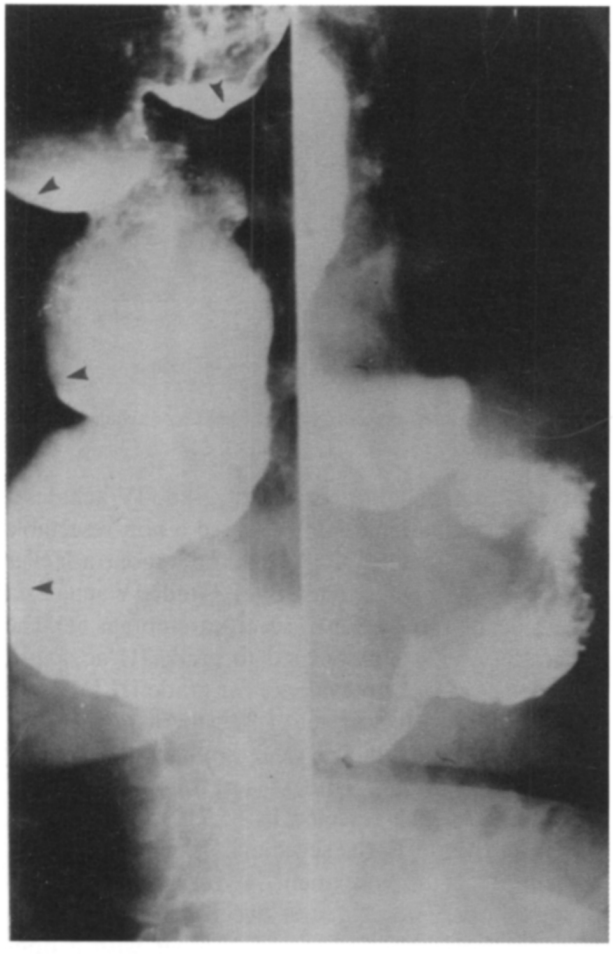

Fig. 4 Huge dolicomegaesophagus with several 'knees' and complete atony (grade IV).

with an Olympus PW 5V 52311 catheter spray after aspirating the retained liquid and cleaning the esophagus with acetic acid.

Evolution

The symptoms had begun less than 5 years before in 37 out of 76 patients, between 5 and 10 years before in 17 out of 76 patients, more than 10 years before in eight out of 76 patients and more than 20 years before in 14 out of 76 patients.

Treatment

All 76 patients underwent surgical treatment. Heller plus antireflux technique was performed in 60 out of 76 patients; nine out of 76 received esophagectomy; five out of 76 underwent a remyotomy plus antireflux procedure; one case underwent a Wendel operation, and one, a cervicotomy plus biopsy.

Laparoscopic myotomy was performed in 10 out of 60 patients treated with Heller plus antireflux technique; nine out of 76 patients were operated on for recurrent achalasia. Complementary surgical procedures to myotomies were: cricopharyngeal myotomy, one case; duodenal diversion, one case, and selective proximal vagotomy, one case. Biliary lithiasis was observed in 11 out of 76 (14.47%) of the patients.

Pathology

Nine surgical specimens from achalasia patients were studied; six of them were associated with squamous cell carcinoma.

a) The specimens were laid on a cork surface and were stained before fixation with 2% Lugol's solution.
b) Photographs were taken.
c) The specimens were fixed in 10% formaldehyde, longitudinal parallel slices 0.5 cm wide were cut including the main lesion (tumor) and the associated lesions.
d) Resection borders and resected nodes were analyzed.
e) The sections were embedded in paraffin and histologic sections were stained with hematoxilyn-eosin and Mason's trichrome.

The following items were considered in the macroscopic evaluation of the specimens:

a) tumor size.
b) location.
c) macroscopic type.
d) identification of lesions close or distant from the main tumor by direct visualization or by staining with 2% Lugol's solution.

There was a seventh case of achalasia with cancer. This case was evaluated only by the endoscopic biopsy sample.
In the microscopic evaluation the following items were considered:

a) Histologic type.
b) Infiltration level of the esophageal wall.
c) Presence of lymphatic and/or vascular emboli.
d) Lymph-node metastasis.
e) Dysplastic lesions.
f) Characteristics of esophagitis.

A minimum of 21 and a maximum of 30 samples were evaluated in each specimen.

RESULTS

Radiology (barium swallow)

Grade II achalasia was diagnosed in 38 (50%) patients; 27(35.53%) were classified as having grade III achalasia, 10 (13.16%) as grade IV, and only one (1.31%) as grade I.

Videoendoscopy

Lugol-negative endoscopic areas (Fig. 5) were found in 10 out of 18 patients; four out of 10 were carcinomas,

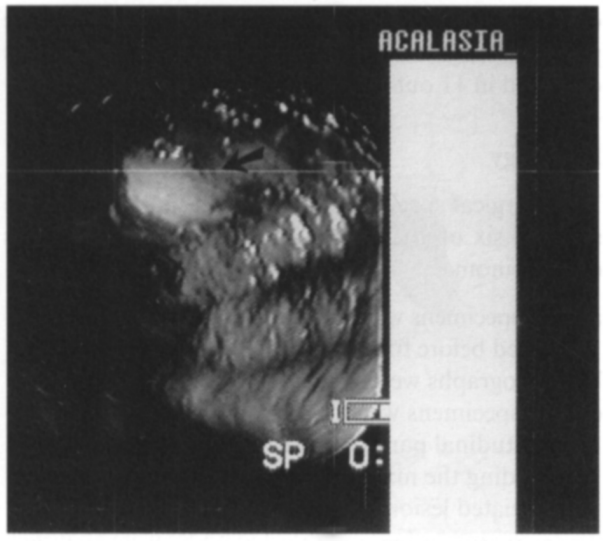

Fig. 5 Lugol negative endoscopic area.

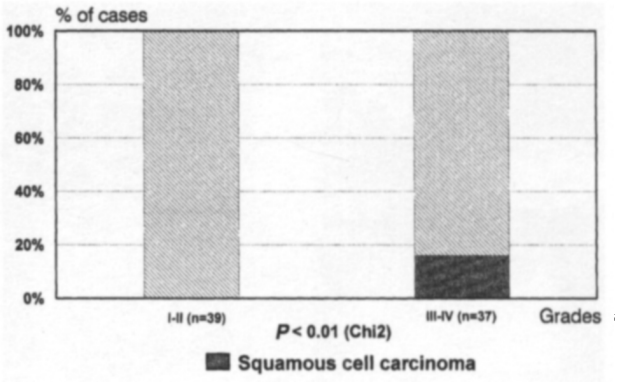

Fig. 6 Prevalence of cancer in different grades of achalasia.

two out of four (cases two and seven) were circular superficial erosive lesions, one out of four was an elevated multifocal lesion less than 1 cm diameter (case three) and the last one presented a longitudinal central ulcer less than 1 cm diameter (case five). In the remaining six out of 10 patients the diagnosis was esophagitis.

Manometry

In 57 out of 76 patients, the diagnosis of achalasia was confirmed by esophageal manometry. This study was not done in two cases because of advanced cancer; it could not be performed in the other eight grade IV achalasia patients nor in nine out of 27 grade III achalasia cases, because it was either impossible to get through the esophagogastric junction with the catheter or because of patient's discomfort.

Cancer and achalasia

In seven patients achalasia was associated with squamous cell carcinoma. (Table 1) Cancer prevalence was seven out of 76 (9.21%); five were males and two females. The mean age was 59 years with a range from 39 to 69 years. Five out of seven cancer patients were more than 60 years old. Six were diagnosed preoperatively; one in situ lesion was found in a surgical specimen of a patient operated of grade IV achalasia (case four). A patient who presented a non-resectable lesion in the upper esophagus had undergone a Heller myotomy a year before (case one). Grade IV achalasia was associated to six out of seven carcinomas and the remaining one was associated to grade III achalasia (case three). Cancer prevalence for grade III/IV achalasia was 18.92% (seven out of 37 patients) (Fig. 6).

Esophagectomy and cervical esophagogastrostomy were performed in six out of seven cancer patients. Tumours could be resected in 85.71% of the cases. The survival rate of the seven achalasia patients with cancer is to date: one patient, 4 years; one patient, 3 years; two patients, 2 years, two other patients survived for less than 1 year and another with a non-resectable tumor died 3 months later.

Pathology

Macroscopic evaluation

The six specimens with carcinoma, presented marked dilation of the esophageal circumference, a thickened and rough mucosa and millimetric erosions (Fig. 7). On transverse section marked hypertrophy of the muscle layer could be observed. The most frequent macroscopic characteristic was the superficial erosion (three out of six, cases two, four and seven), in two of these cases the lesion was 5–8 cm diameter, and in one it was 1 cm diameter. Lugol's solution staining was negative in ulcer and erosion areas.

In two cases synchronic tumors were found (cases three and six). In one case (case three), an irregular ulcer in the lower third (T2 N0 M0) and an elevated

Table 1 Clinical and pathologic data on patients with achalasia and carcinoma

CASE	AGE	SEX	LOCATION	SYMPTOMS	GRADE	T.N.M.
1	49	M	UPPER	> 20 YEARS	IV	T4.N1.M0.
2	69	M	MID	5 YEARS	III	T1.N0.M0.
3	39	M	MID and INF	> 20 YEARS	IV	T2.N0.M0.
4	63	F	UPPER	> 30 YEARS	IV	T1.N0.M0.
5	63	F	MID	> 30 YEARS	IV	T1.N0.M0.
6	61	M	MID	> 30 YEARS	IV	T3.N1.M0.
7	69	M	MID	> 30 YEARS	IV	Tis.N0.M0.

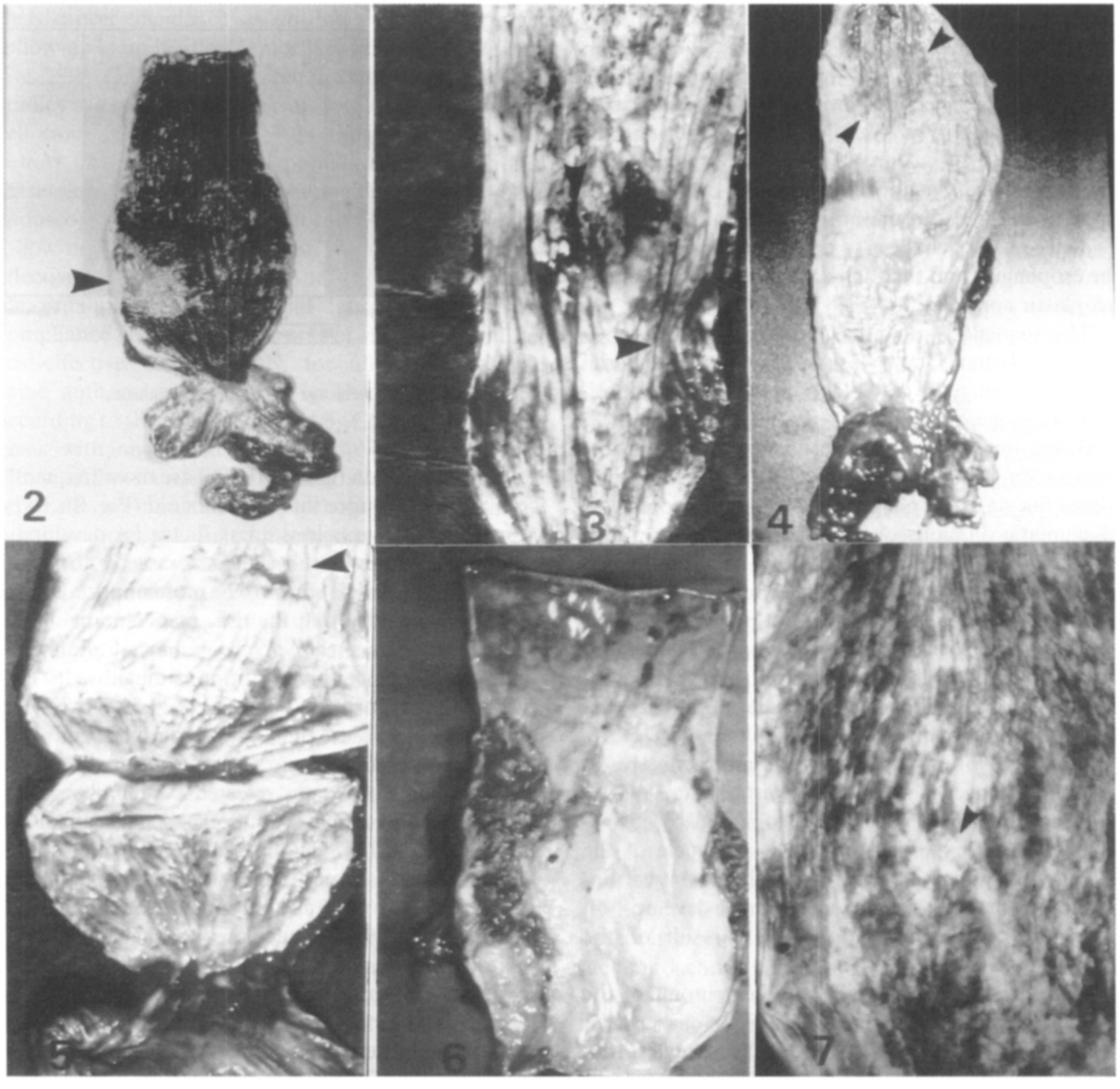

Fig. 7 Resected specimens with cancer in achalasia. Cases 2,3,4,5,6 and 7.

lesion associated with an irregular erosion in the middle third (T1 N0 M0) (Fig. 7). In the other case (case six), an irregular ulcer with elevated and irregular borders in lower third (T3 N0 M0) and regular ulcer 4 cm away from the other one ($T1_{SM}$) (Fig. 7).

Microscopic evaluation

Histologic evaluation showed moderately differentiated squamous cell carcinoma in all samples. High-grade dysplasia was observed in four cases (cases three, five, six and seven) and low-grade dysplasia was found in one case (case three); this finding was always located close to the squamous cell carcinoma. Lymphatic neoplastic emboli and positive nodes were found in only one case (case six). Venous emboli were observed in none of the specimens.

In every case the accompanying esophagitis was characterized by acanthosis with isolated areas of atrophy associated with reepithelized erosions; papillomatosis and infiltration of the epithelium by polimorphonuclear leukocytes; marked papillary congestion and chronic inflammatory infiltrate that reached the muscularis propria and adventitia layers; areas of submucosal and mucosal fibrosis, probably cicatricial sequelae of ulcers. In three cases perinuclear halos in keratinocytes were observed (coilocytosis).

DISCUSSION

In 1872, C.H. Fagge described a carcinoma involving the esophageal body in an autopsy of an 84-year-old patient with a history of more than 40 years of

dysphagia, which he thought was caused more by benign appearing stricture of the distal esophagus than by cancer.[17] That was the first time in which the relationship between achalasia and esophageal carcinoma was established. However, the difference in the incidence and prevalence reported[13,18,19] makes some authors believe that this association is overestimated in literature.[14,20,21] From another point of view, much evidence relates achalasia to epidermoid carcinoma of the esophagus, and thus achalasia is considered a preneoplastic condition.[8,10,18,22,23]

The sequence would be as follow: Achalasia → esophageal retention → stasis esophagitis → bacterial overgrowth increase and stagnant food descompotition → chronic esophagitis → dysplasia → cancer.

Based on this potential sequence many authors worked on preventive approaches with early treatments for stasis esophagitis by means of esophageal phenumatic dilations or surgery.[24–26] However, many reported cases on cancer in achalasia had been treated with bouginage for many years.[7,22] Surgical treatment appears to be more effective in preventing stasis esophagitis.[22,24] Nevertheless, this approach does not prevent cancerous lesions as proved by the development of esophageal cancer in achalasia patients that had undergone myotomy more than 10 years before.[23,27] Myotomy appears to be more effective in preventing cancer in a non-dilated esophagus.[23,25,28]

Adenocarcinoma is achalasia is caused by gastroesophageal reflux, which in turn is a sequela of the achalasia treatment[29] (pneumatic dilation or cardiomyotomy, or both). Adenocarcinoma develops on a Barrett's esophagus and not as a result of the achalasia.[30,31]

In achalasia patients, epidermoid carcinoma of the esophagus begins as an average 10 years earlier than in the general population.[8] Some authors suggest that this fact would support the association between cancer and achalasia.[8] In Argentina, esophageal cancer is more frequent among 65–75-year-old patients;[32] our patients with cancer and achalasia had a mean age of 59-years-old.

Other authors also point out that the tumor localization in achalasia patients is more frequent in the middle third of the esophagus.[25,33] In five out of seven of our cancer patients the tumor was located in the middle third, the other two were in the upper third. This last localization was also observed by other authors[34] and would disagree with the theory that the localization in the middle third is coincident with the upper level of stasis.

Goldblum observed that stasis esophagitis is present in all the esophageal mucosa.[35] Esophageal enlargement is described in all reported cases,[2,23] that is to say, in advanced stages of the disease. Our seven cancers developed over enlarged esophagus. Cancer prevalence in grade III and IV achalasia was 18.92% (Fig. 6). It is important to underline that advanced

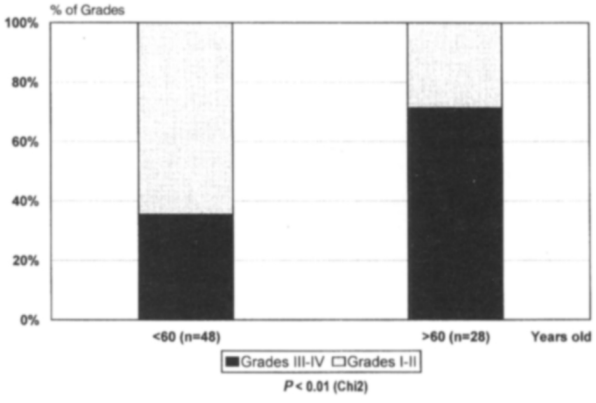

Fig. 8 Relation between age and grade of achalasia.

stages of achalasia (grades III/IV) are most frequently seen in patients more than 60 years old (Fig. 8). To be more than 60 years old is a risk factor for developing esophageal cancer, but in achalasia patients the duration of the dysphagia seems to be more important.[7] We agree with the idea that the time of evolution should be calculated since the very beginning of the symptoms and not since this condition is diagnosed.[26] The average time reported in literature is 20.5 years.[7,27,28] In our series, it was more than 20 years in six out of seven patients, more than 30 years in four out of seven, and the remaining one only referred 5-year symptoms. Cancer was observed in six out of 14 achalasia patients with more than 20 years of evolution.

Our series is formed only by patients operated of achalasia at a referral for surgery of esophageal diseases. The incidence calculated for this group could overestimate the real incidence of cancer is achalasia.[26] In our series the prevalence of cancer in achalasia was seven out of 76 or 9.21%.

If one considers the patients with grade III and IV achalasia of Resano's classification, esophageal enlargement, and more than 20 years of evolution, cancer prevalence will be higher in this group than in the global prevalence published by different authors.[2,7,8,22,23,25,28,34]

This should be considered a high risk group of developing cancer in achalasia. In addition, it is advisable to take into account other common risk factors of esophageal cancer, such as being more than 60 years old, and alcohol and cigarette consumer.[25] The five men in our series did smoke and drink alcohol, but neither of the two women did. For several reasons achalasia patients with cancer are usually diagnosed late in the course of their disease. Long-term dysphagia and esophageal enlargement are probably contributing factors. This condition presents low operability and resectability rates, as well as a low 5-year-survival rate;[25,33,34] thus, any effort to reach early diagnoses is vital.[28]

There is much controversy about the need of surveillance in achalasia patients. Some authors believe

that cancer incidence is so low that endoscopic follow-up is unjustified[14] since it is fallible and expensive.[20,26,34] On the other hand, recent prospective studies suggest that the risk of developing squamous cell carcinoma would be 3–33 times higher in this cohort than in the general population.[7,36] Therefore, these authors propose a surveillance with Rx, endoscopy and cytology every 1 or 2 years. This follow-up should meet certain requirements to be effective[34], i.e. a) to be able to identify small mucosal abnormalities even superficial lesions; b) patient's compliance should be high, and c) studies should be cost-effective. Consequently, for all these reasons, some authors suggest using brush-cytologic studies according to the results reported by Chinese authors in areas with high incidence of esophageal cancer.[34,37] Other authors consider that this surveillance would represent an unnecessary psychological trauma to achalasia patients. In addition, they think that the cost-effectiveness ratio and safety rate of this approach are low.[14] On the contrary, we consider that it would be useful in achalasia patients with high risk of developing cancer, such as those with advanced disease (grades III/IV) with more than 20 years of evolution, especially if they are more than 60 years old, smokers and drink alcohol. In our opinion, these patients should be yearly controlled by endoscopy and vital staining.

Resection is indicated in grade IV achalasia patients[38,39] and in those grade III cases with preneoplastic endoscopic lesions. It is particularly important to follow this group of patients. In these cases surgical resection can be considered a definite treatment with a good life expectancy and a reasonable surgical risk.

Esophagitis associated with achalasia is characterized by the presence of a rough thickened and eroded mucosa along the whole dilated esophagus, with parietal thickening caused by hypertophy of the muscularis propia. Histologic studies show achantosis, papillomatosis, transmural inflammatory chronic infiltrate, erosions and ulcers with submucosal cicatricial fibrosis. Unfortunately, few studies describe the characteristics of esophagitis associated with achalasia; the ones that do so mention leukoplacia, epithelial hyperplasia and papillomas. Similarly, there are few references to the presence of dysplasia[40] or to the macroscopic appearance of carcinomas associated with achalasia.[7] In an extensive morphologic study on 42 surgical specimens, Goldblum describes macroscopic and morphologic alterations similar to those observed by us. He found two cases with dysplasia, one case with high-grade dysplasia on squamous epithelium and the other one with low grade dysplasia on a Barrett's esophagus caused by postmyotomy reflux.[35] This author also reports a case of squamous cell carcinoma with superficial invasion. Neither Goldblum's study nor others[5,35] described erosions and/or ulcers in esophagitis associated with achalasia as we frequently found.

Reports on cancer in situ in achalasia are infrequent, as well as long-term survival rates. We diagnosed four early carcinomas, three of them associated with high and low grade dysplasia near the lesion.

These findings in achalasia are similar to those observed in other preneoplastic conditions, suggesting the sequence esophagitis-dysplasia-cancer and supporting the hypothesis of the multicentric and field carcinogenesis as the main origin of squamous cell carcinoma also in achalasia.[41,42,43]

On the other hand, the high frequency of ulcers and/or erosions with irregular borders in cancer associated with achalasia is surprising, as well as the fact that three out of four early lesions presented erosions. In China, Liu et al. reported a higher frequency of erosive and superficial types of lesions among 150 surgical specimens for early esophageal carcinomas.[44]

Vital stainings, as toluidine blue or Lugol's solution, identify dysplastic lesions and early carcinoma.[45–47] These are highly sensitive techniques, but their specificity is not 100%, since areas of immature-regenerative epithelium in esophagitis present the same staining characteristics of achalasia, as happened with six out of 18 of our cases. We recommend the endoscopic screening of dysplastic lesions with vital stainings with Lugol's solution[48] and the routine biopsy of any erosive or ulcerated lesion in the follow up of patients affected by this preneoplastic condition.

Achalasia is considered a preneoplastic disease, but it has not been tested yet with biological markers as Barrett's esophagus. Recently, Porschen advised the use of flow cytometry based on the study of a specimen of cancer associated with achalasia.[40] The most appropriate approach in the future seems to be to define more clearly the high risk group among achalasia patients and to perform their follow up with endoscopy, lugol's vital staining and biological markers.

Those patients more than 60 years old with grade III or IV achalasia with more than 20 years of evolution present a higher risk of developing esophageal cancer. Therefore, it is advisable to follow them up endoscopically once a year with special esophageal staining[49] to identify esophageal flat or superficial lesions as occurred in four of our cases. It is true that to diagnose cancer in achalasia several endoscopies are required, but it is also true that this condition is at least 16 times more frequent[26] in an esophagus with achalasia than in a normal esophagus. It is mandatory to perform thorough studies to detect flat and superficial lesions with discoloration or Lugol-negative areas, dysplastic lesions and early esophageal cancer in cases of grade III/IV achalasia. This approach can change the natural course of the disease and improve survival rates.

Although our study addresses prevalence, since we have not undertaken surveillance, many of our patients had been studied by other institutions during their course and only two cases were referred to surgery with cancer in achalasia diagnosis.

Prevalence can change according to each institution and to the number of years considered. The number of patients and the fact of being a referral center for esophageal surgery do not allow us to draw general conclusions, but our findings underline the importance of searching superficial lesions to perform early diagnosis.

CONCLUSIONS

Achalasia of the esophagus is a well-known preneoplastic disease with more risk of developing cancer than in general population. This risk is even higher in achalasia patients with more than 20 years of symptoms and advanced achalasia, enlargement of the esophagus, 'knees' and marked retention. This group of patients, in which surveillance with endoscopy and vital staining should be performed, must be considered of high risk to develop cancer in achalasia. In addition, it is advisable to take into account other common risk factors of esophageal cancer, such as being more than 60 years old, and an alcohol and cigarette consumer.

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