Clin Rheumatol (2004) 23: 516–522
DOI 10.1007/s10067-004-0940-5

ORIGINAL ARTICLE

**David Launay · Rozenn Le Berre · Pierre-Yves Hatron
Jean-Philippe Peyrat · Eric Hachulla · Bernard Devulder
Mohamed Hebbar**

Association between systemic sclerosis and breast cancer: eight new cases and review of the literature

Received: 14 October 2003 / Accepted: 2 April 2004 / Published online: 2 June 2004

Abstract Several studies have demonstrated an increased frequency of cancer in patients with systemic sclerosis (SSc), specially lung and breast cancers. The pathogenesis of the association between SSc and cancer is not fully established. The aim of this study was to describe new cases of the association between SSc and breast cancer and to perform a review of the literature. We retrospectively studied the medical files of eight patients followed in our institution for SSc and breast cancer. We analyzed them with data available in the literature for a total of 46 patients. Cutaneous extension of SSc was clearly mentioned in 17 cases: the SSc was limited in 10 cases and diffuse in 7 cases The median age at the diagnosis of cancer was 54 years (range: 40–71). The median duration between SSc onset and breast cancer diagnosis was 11.5 months (range: 0–288). The duration between SSc onset and breast cancer diagnosis was ≤ 12 months in 27 of 44 patients (61.4%), and in 11 (25%) of them the diagnosis of both diseases was made simultaneously. It was clearly mentioned for 35 patients whether the diagnosis of breast cancer was made before or after the onset of SSc. The diagnosis of breast cancer was made before SSc onset in 17 of 35 patients (48.6%) and after SSc onset in 18 of 35 patients (51.4%). For 33 patients, the follow-up was available: 18 (54.5%) died, 11 (33.3%) of them within the 1st year after the diagnosis of the cancer. For none of the patients did the anticancer treatment improve the SSc. The close temporal relationship between SSc onset and breast cancer diagnosis is highly suggestive of a pathophysiological link. SSc is probably not a paraneoplastic disease since the anticancer treatment has no influence on the evolution of SSc. However, it can be suggested that SSc could be a disease facilitating breast cancer and/or metastases development.

Keywords Breast cancer · Endothelial cells · E-selectin · Systemic sclerosis

Introduction

Systemic sclerosis (SSc) is a connective tissue disease involving the skin and internal organs. SSc is characterized by fibroblast activation and collagen deposition, immune abnormalities and endothelial cell lesion and activation [1, 2]. Several studies have focused on the higher frequency of cancers in patients with SSc than expected in the general population [3, 4, 5]. The main cancers found are lung and breast cancers [4, 5, 6, 7, 8, 9]. Some authors have suggested that SSc could be considered a paraneoplastic syndrome since both diseases occur most often in close temporal relationship [6, 8, 9]. However, this remains controversial and pathogenesis of this association is still not fully understood.

The aim of this study was to describe new cases of the association between SSc and breast cancer and to perform a review of the literature. We also discuss further the potent pathophysiological link between both diseases.

Patients and methods

We have retrospectively studied the medical files of 203 consecutive patients followed between January 1990 and December 2002 in the Department of Internal Medicine of the Claude-Huriez Hospital, Lille, France who fulfilled the ACR criteria for SSc [10]. We selected the

The first two authors have contributed equally to this work

D. Launay · R. Le Berre · P.-Y. Hatron · E. Hachulla
B. Devulder · M. Hebbar (✉)
Service de Médecine Interne, CHRU, Hôpital Claude Huriez,
1 Place Verdun, 59037 Lille, France
E-mail: m-hebbar@chru-lille.fr
Tel.: +33-3-20445479
Fax: +33-3-20445023

J.-P. Peyrat
Laboratoire d'Oncologie Moléculaire Humaine,
Centre Oscar Lambret, Lille, France

patients with a history of breast cancer either before or after the SSc onset. The following data were recorded: date of birth, cutaneous extension of SSc according to the subset classification criteria [1], date of SSc onset defined by the beginning of Raynaud's phenomenon, and results of the chest computed tomodensitometry, the echocardiography, and the search for antinuclear antibodies. We also reported on the follow-up and the cause death. For breast carcinoma, we recorded the following data: date of diagnosis, histoprognostic grading (HPG) according to the Scarff and Bloom criteria [11], nodal involvement, search for hormonal receptors, and treatment.

We performed a review of the literature about the association between SSc and breast cancer. We used the PubMed system to do a MEDLINE search using the mesh terms "breast neoplasm" and "scleroderma, systemic." We selected the cases with sufficient details to allow an analysis. In particularly, we focused on sex of the patients, age at diagnosis of breast cancer, and interval between diagnosis of both diseases, death during follow-up, and type of SSc according to the subset classification criteria. We also recorded the result of the anticancer treatment.

Results

We found eight women with the association of SSc and breast cancer among the 203 patients (3.9%) followed in our institution between January 1990 and December 2002.

Patient 1

In January 1994, a 56-year-old woman underwent a total left mastectomy for an invasive breast adenocarcinoma. There was evidence of nodal involvement in 3 of 18 axillary lymph nodes. By immunohistochemistry, the search for hormonal receptors was positive for estrogen and negative for progesterone. The HPG was grade II. Surgery was followed by external radiotherapy, chemotherapy [six courses of FEC regimen (cyclophosphamide, epirubicin, and 5-flurouracil)] and hormonal therapy (tamoxifen 20 mg/d).

She was referred to our institution in March 1994 because of a worsening thickening of the skin and a Raynaud's phenomenon that had begun about 18 months before the diagnosis of the breast cancer. On physical examination, there was a thickening of the skin over the arms, feet, and face highly evocative of diffuse cutaneous SSc. The patient did not complain about dyspnea or esophageal reflux. A chest computed tomodensitometry showed a pulmonary fibrosis. Echocardiography did not show any pulmonary hypertension. Search for antinuclear antibodies was negative. Diffuse cutaneous SSc was diagnosed and oral prednisolone 1 mg/kg per day was begun because of severe impairment of joint mobility due to skin thickening. Unfortunately, the improvement was short and D-penicillamine was started 2 months later. After 1 year, the SSc was stable, but the patient was admitted to hospital for a retroperitoneal carcinosis. The metastases progressed rapidly and the patient died from renal failure.

Patient 2

A 65-year-old woman, with a history of right node-negative breast adenocarcinoma treated by mastectomy and radiotherapy 20 years ago, was referred in February 2000 for suspicion of SSc. She presented Raynaud's phenomenon for 2 years. She did not complain about arthralgia, dyspnea, esophageal reflux, or dysphagia. Physical examination showed sclerodactyly but no telangiectasia. The esophageal manometry was normal. Bilateral hand radiograms showed no calcinosis. Search for antinuclear antibodies was strongly positive with an anticentromere pattern. Chest computed tomodensitometry showed a pulmonary fibrosis evocative of SSc but associated with hilar nodes and moderate bilateral pleural effusion. Echocardiography was normal. Limited cutaneous SSc was diagnosed. Histological examination of pleural aspirate showed adenocarcinomatous cells. By immunohistochemistry, search for hormonal receptors was positive for estrogen and negative for progesterone. Six courses of FEC regimen and tamoxifen (20 mg/day) were started. Then, three courses of paclitaxel and finally eight courses of vinorelbine until March 2001 were necessary to control the cancer. Currently, there is no evidence of cancer progression. Sclerodactyly and Raynaud's phenomenon are also stable.

Patient 3

In February 1984, a 62-year-old woman was referred for sclerodactyly and recent Raynaud's phenomenon. Bilateral hand radiograms showed no evidence of calcinosis. Esophageal manometry showed evidence for esophageal involvement evocative of SSc. Search for antinuclear antibodies was negative. Chest X-ray revealed mild basal fibrosis. Limited cutaneous SSc was diagnosed. Eight months later, the patient underwent a right mastectomy for a breast carcinoma (positive hormonal receptors for estrogen and progesterone, HPG II, lack of axillary nodal involvement). Surgery was followed by external radiotherapy. The patient was lost to follow-up.

The patient was admitted for dyspnea in June 1997. Chest computed tomodensitometry showed bilateral basal fibrosis with pleural nodes and mediastinal adenopathies. Mediastinoscopy was not performed because of the impaired clinical status. CA 15-3 concentration was 104 IU/ml (normal: <25 IU/ml). Treatment with tamoxifen (20 mg/day) was begun and the CA 15-3 concentration decreased to 51 in May 1998. Cutaneous

extension of SSc was stable and considered limited. In November 1998, the dyspnea increased and was associated with bilateral pitting edema and pleural effusion. Echocardiography revealed a severe pulmonary arterial hypertension (systolic pulmonary artery pressure: 75 mmHg) and right cardiac failure. The abdominal ultrasound examination revealed no metastases. The patient died from respiratory failure in January 1999.

Patient 4

A 53-year-old woman had undergone a breast tumorectomy with axillary dissection for a node-negative adenocarcinoma in June 1989 (lack of hormonal receptors, HPG III). Surgery was followed by external radiotherapy. She was referred in October 1996 because of a worsening Raynaud's phenomenon which had begun in October 1994. There was sclerodactyly and pitting scars. Search for anti-Scl-70 antibodies was positive. Limited cutaneous SSc was diagnosed. She received treatment with a calcium blocker (nifedipine) and refused more investigations. She was lost to follow-up until April 1998 when she presented with stable sclerodactyly and arthralgia affecting the wrist. She also complained about dyspnea but did not mention any esophageal reflux. Chest computed tomodensitometry revealed bilateral basal fibrosis. Echocardiography did not show any pulmonary arterial hypertension. D-penicillamine was started but rapidly replaced by colchicine because of allergic manifestations. In September 1999, she complained again about arthralgia affecting the wrist and the ankle. Sclerodactyly was stable. Hydroxychloroquine associated with prednisolone (10 mg/day) was started. Currently, there is no evidence of tumor relapse and SSc is stable.

Patient 5

A 54-year-old woman was referred in April 2000 for Raynaud's phenomenon which had begun in November 1999. In June 1999, she had undergone left breast tumorectomy with axillary dissection for a node-negative breast adenocarcinoma (HPG III, presence of estrogen and progesterone hormonal receptors). Surgery was followed by external radiotherapy and hormonal therapy (tamoxifen: 20 mg/day). Clinical examination showed sclerodactyly with pitting scars. The patient complained about arthralgia. There was neither calcinosis nor telangiectasia. There was no evidence of gastroesophageal involvement on esophageal manometry. Speckle-patterned antinuclear antibodies were strongly positive without any specificity. Chest computed tomodensitometry did not show any pulmonary fibrosis. Echocardiography did not show any evidence of pulmonary arterial hypertension. We concluded that the patient had a limited cutaneous SSc without evidence of visceral involvement. In December 2000, prednisolone (30 mg/day) was started for lower limb arthralgia. Although the prednisolone daily dose was rapidly decreased, the patient experienced an acute renal crisis in March 2001. Angiotensin-converting enzyme inhibitors (captopril: 100 mg/day) were used without any efficacy and hemodialysis was begun. Currently, the patient still needs dialysis. There is no evidence of cancer progression.

Patient 6

A 61-year-old woman was followed for limited cutaneous SSc since 1993. She had severe Raynaud's phenomenon, sclerodactyly with ulcers, calcinosis, esophageal involvement, and multiple telangiectasia on the face and hands. Search for antinuclear antibodies was strongly positive with an anticentromere pattern. Chest computed tomodensitometry did not show any pulmonary fibrosis. Limited cutaneous SSc was diagnosed. Treatment included buflomedil and aspirin. In 1999, the patient complained about severe dyspnea. Chest computed tomodensitometry did not show any pulmonary fibrosis. Doppler echocardiography revealed severe pulmonary arterial hypertension, which was confirmed by right heart catheterization (mean pulmonary artery pressure: 55 mmHg). Aerosolized Ilomedine and oral anticoagulant improved cardiopulmonary hemodynamics and dyspnea. In August 2001, clinical examination showed two tumors in the left breast whose biopsy revealed a breast adenocarcinoma (HPG I, presence of estrogen and progesterone hormonal receptors). The patient underwent a total left mastectomy with axillary dissection in September 2001. No nodal involvement was found. Six courses of FEC were started. SSc was still active with severe sclerodactyly and a worsening of pulmonary hypertension (systolic pulmonary artery pressure: 85 mmHg) which is now treated with the endothelin receptor inhibitor bosentan.

Patient 7

A 60-year-old woman presented in July 2001 with a 2-year history of Raynaud's phenomenon affecting the first, second, and third fingers of the right hand. In July 2000, she had undergone a left breast tumorectomy with axillary dissection for a node-negative breast adenocarcinoma (HPG I, presence of estrogen and progesterone receptors). Surgery was followed by external radiotherapy of the left breast and hormonal therapy (tamoxifen: 20 mg/day). A recent control did not show any evidence for cancer progression. Clinical examination showed sclerodactyly and pitting scares on the three fingers affected by Raynaud's phenomenon. There was neither calcinosis nor telangiectasia. The patient did not complain about gastroesophageal reflux. Anticentromere antibodies were present. Chest computed tomodensitometry did not show any pulmonary fibrosis. Doppler

echocardiography was normal. Altogether, these findings were consistent with a limited cutaneous form of SSc. In September 2001, buflomedil and aspirin were started. Currently, SSc is stable and there is no evidence of cancer progression.

Patient 8

A 44-year-old woman was first admitted for dyspnea in July 2001. She complained for 5 years about Raynaud's phenomenon. Physical examination showed sclerodactyly and esophageal reflux. Chest computed tomodensitometry disclosed a diffuse pulmonary fibrosis evocative of SSc. Search for anti-Scl 70 was positive. Limited cutaneous SSc was diagnosed. D-penicillamine was started. Three months after, a right breast carcinoma was disclosed and the patient underwent a total right mastectomy for an adenocarcinoma HPG II with involvement of 1 of 19 axillary lymph nodes and presence of estrogen and progesterone receptors. Because of SSc and pulmonary fibrosis, no radiotherapy was performed. Tamoxifen was started. One year later, dyspnea was still present. Echocardiography and right heart catheterism showed a precapillary pulmonary hypertension. Oral bosentan was started. Currently, 3 months after bosentan was started, dyspnea and SSc are stable and there is no evidence of cancer progression.

Review of the literature

A review of the literature allowed us to find 60 cases of the association between SSc and breast cancer [4, 5, 8, 9, 12, 13, 14, 15, 16, 17]. Among these patients, 38 were described with sufficient detail to allow analysis. With our additional eight patients, we are therefore able to describe 46 patients (Table 1).

All of them were female. The median age at the diagnosis of cancer was 54 years (range: 40–71). Cutaneous extension of SSc was clearly mentioned in 17 cases, according to the subset classification criteria. The SSc was limited in ten cases and diffuse in seven cases. The median duration between SSc onset and breast cancer diagnosis was calculated in the 40 patients for whom these data were clearly mentioned and was 11.5 months (range: 0–288). The duration between SSc onset and breast cancer, whatever the order of occurrence, was ≤ 12 months in 27 of 44 patients (61.4%), and in 11 (25%) of them the diagnosis of both diseases was made simultaneously. The two remaining patients are those from the study of Abu-Shakra et al. [8] for whom these data are not available. It was clearly mentioned for 35 patients whether the diagnosis of breast cancer was made before or after the onset of SSc. The diagnosis of breast cancer was made before SSc onset in 17 of 35 patients (48.6%) and after SSc onset in 18 of 35 patients (51.4%). For 33 patients, the follow-up was available: 18 (54.5%) died, 11 (33.3%) of them within the 1st year after the diagnosis of the cancer. Unfortunately, the exact cause of the death (SSc or breast cancer or other) was rarely mentioned in the literature (Table 1). For none of the patients was it firmly established that the anticancer treatment improved the SSc.

Discussion

We report on eight new cases of the association between SSc and breast cancer. Four epidemiological studies have focused on the association between SSc and cancer [3, 4, 6, 8]. For Rosenthal et al. [6], the standardized incidence ratio (SIR) for developing cancer for patients with SSc was 1.5 [95% confidence interval (CI): 1.2–1.9]. For Roumm et al. [4], the calculated relative difference (observed/expected cancer) was increased at 1.81 in SSc. For Abu-Shakra et al. [8], the age-standardized incidence rate for all cancers in the SSc population was 2.1 times the overall rate in the reference population. Finally, the most recent population-based cohort study showed a significantly increased SIR for all cancers (1.99, 95% CI: 1.46–2.65) [3]. However, as in Rosenthal's study [6], Hill et al. did not find that the increased SIR of breast cancer (1.62, 95% CI: 0.7–3.19) reached statistical significance [3]. However, there was a small number of patients ($n = 8$). All these studies favor a higher risk of cancer, especially lung cancer, in patients with SSc but there is always a doubt concerning breast cancer.

In our study, we found a close temporal relationship between SSc onset and breast cancer diagnosis. Up to 25% of patients have even the diagnosis of breast cancer made simultaneously to the SSc onset. This is strongly suggestive of a pathophysiological link between these two conditions. Firstly, one can suggest that SSc is a paraneoplastic syndrome. However, we did not find any clear evidence either in our cases or in the literature that the treatment or removal of the breast cancer had led to any healing or great improvement of SSc manifestations. This is a strong argument against the paraneoplastic nature of SSc. Secondly, one can suggest that in cases where SSc occurs shortly after treatment of the cancer chemotherapy or radiotherapy may be associated with the development of SSc [18]. Davies et al. [19] described six patients with breast cancer developing localized scleroderma within their radiation port. Darras-Joly et al. reported three patients who developed SSc after ionizing irradiation for nasopharyngeal carcinoma (two patients) and for breast carcinoma (one patient) [15]. Conversely, Ross et al. [20], in a matched pair control study with 61 patients without collagen vascular diseases and 61 patients with vascular diseases (4 SSc), did not observe a significant increase in radiation therapy complications for patients with collagen vascular diseases. Moreover, radiotherapy would hardly explain Raynaud's phenomenon or antinuclear antibodies found in our patients and in the great majority of patients in the literature. Cyclophosphamide is one of the treatments of SSc that could increase the occurrence of breast

Table 1 Review of the literature about the association between systemic sclerosis and breast cancer. *SSc* systemic sclerosis, *NM* not mentioned, *BC* breast cancer

References	Study	Number of SSc	Number of BC	Age at diagnosis of BC (years)	Interval between both disease onsets (months)	Order of occurrence of both diseases[a]	Type of SSc	Death during follow-up	Cause of death
Duncan et al. [3]	Retrospective cohort	2141	16	68	< 12	2	NM	Yes	NM
				61	24	2		Yes	
				62	36	1		No	
				46	48	1		Yes	
				43	36	2		Yes	
				49	72	1		Yes	
				61	Simultaneous	-		Yes	
				58	Simultaneous	-		Yes	
				56	Simultaneous	-		Yes	
				55	Simultaneous	-		Yes	
				50	24	2		Yes	
				50	12	1		Yes	
				43	24	2		No	
				51	12	1		Yes	
				32	Simultaneous	-		No	
				41	96	1		No	
Roumm et al. [4]	Retrospective cohort	262	5	58	Simultaneous	-	NM	NM	NM
				41	6	2			
				40	24	2			
				57	2	2			
				67	Simultaneous	-			
Abu-Shakra et al. [7]	Retrospective cohort	248	5	NM	< 6	2	NM	NM	NM
					< 6	2			
					< 6	1			
					> 6	1			
					> 6	2			
Lee et al. [8]	Retrospective cohort	95	4	51	24	2	Diffuse	No	other
				53	24	2	Diffuse	Yes	BC
				49	6	1	Limited	Yes	
				57	Simultaneous	-	Limited	No	
Talbott et al. [11]	Case report	1	1	71	6	1	NM	NM	NM
Forbes et al. (12)	Case report	4	4	58	4	1	Diffuse	Yes	SSc
				47	Simultaneous	-	Diffuse	Yes	BC
				54	11	1	limited	No	
				54	Simultaneous	-	limited	No	
Bielefeld et al. [16]	Case report	1	1	53	288	1	NM	NM	NM
Booton et al. [13]	Case report	1	1	50	6	1	Diffuse	NM	NM
Darras-Joly et al. [14]	Case report	1	1	71	Simultaneous	-	Diffuse	No	
Present study	Case report	8	8	56	18	2	Diffuse	Yes	BC
				65	24	1	Limited	No	SSc and BC
				62	8	2	Limited	Yes	
				53	108	1	Limited	No	
				53	6	1	Limited	No	
				61	96	2	Limited	No	
				59	12	2	Limited	No	
				44	63	2	Limited	No	

[a] 1: breast cancer occurring prior to SSc, 2: SSc occurring prior to breast cancer

cancer. Hesselstrand et al. [21] analyzed the causes of death in 249 patients with SSc, and evaluated the occurrence of cancers and their possible association with oral cyclophosphamide treatment. They failed to find any statistically significant relationship between this treatment and the occurrence of breast cancer. Moreover, none of our patients had received cyclophosphamide before breast cancer was diagnosed.

Thirdly, it is possible that the development of SSc in association with cancer could result from the altered immune response. Anticentromere and anti-Scl-70 antibodies are frequently found in patients with SSc. They are directed respectively against centromere proteins and topoisomerase I which are involved in the structure of DNA. It is therefore suggested that these antibodies could interact with DNA structure and favor develop-

ment of cancer [22]. Indeed, Rattner et al. [22] studied the clinical features of patients with autoantibodies directed against centromere protein CENP-F and the frequency of theses autoantibodies in patients with various diseases (melanoma, breast cancer, SSc and other connective tissue diseases): a high proportion of individuals with CENP-F antibodies had neoplasia. However, the role of these antibodies remains controversial since most studies did not find any association between SSc patients with cancer and subtypes of antibodies [23, 24].

Finally, a pathophysiological link between SSc and breast cancer could be endothelial cell activation. One of the endothelial cell activation markers is the adhesion molecule E-selectin [25]. High tissular expression of E-selectin as well as increased serum concentrations of the soluble E-selectin are found in patients with SSc [26, 27]. Several studies have also suggested an important role for endothelial cells in tumor development and metastasis [28, 29] because endothelial cell activation may increase the metastatic process by facilitating the adhesiveness of tumor cells on endothelial cells in sites distant from the primary tumor. In patients with breast cancer, high preoperative soluble E-selectin concentrations were significantly associated with shorter relapse-free and overall survivals [30, 31]. Furthermore, a direct role of endothelial cells in the primary tumor development cannot be excluded. Some studies have demonstrated a production of growth factors by activated endothelial cells (i.e., fibroblast growth factor, insulin growth factor-2, platelet-derived growth factor, and colony-stimulating factors) [32]. Therefore, one can suggest that the endothelial cell activation observed in SSc could increase tumor development through these different mechanisms. This could also explain the bad prognosis of patients with SSc and breast cancer since up to 33.3% of patients in our study died within the 1st year after the diagnosis of the cancer.

In conclusion, there is a close temporal relationship between SSc and breast cancer onset in most patients, suggesting a pathophysiological link. SSc could facilitate tumor progression and metastases explaining why breast cancer in patients with SSc often has a bad prognosis. This study underlines the necessity of carefully looking for cancer, especially breast cancer, in patients with systemic sclerosis.

References

1. LeRoy EC, Black C, Fleischmajer R, et al. (1988) Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. J Rheumatol 15:202–205
2. Fleischmajer R (1977) The pathophysiology of scleroderma. Int J Dermatol 16:321–328
3. Hill CL, Nguyen AM, Roder D, Roberts-Thomson P (2003) Risk of cancer in patients with scleroderma: a population based cohort study. Ann Rheum Dis 62:728–731
4. Duncan SC, Winkelmann RK (1979) Cancer and scleroderma. Arch Dermatol 115:950–955
5. Roumm AD, Medsger TA Jr (1985) Cancer and systemic sclerosis. An epidemiologic study. Arthritis Rheum 28:1336–1340
6. Rosenthal AK, McLaughlin JK, Gridley G, Nyren O (1995) Incidence of cancer among patients with systemic sclerosis. Cancer 76:910–914
7. Rosenthal AK, McLaughlin JK, Linet MS, Persson I (1993) Scleroderma and malignancy: an epidemiological study. Ann Rheum Dis 52:531–533
8. Abu-Shakra M, Guillemin F, Lee P (1993) Cancer in systemic sclerosis. Arthritis Rheum 36:460–464
9. Lee P, Alderdice C, Wilkinson S, Keystone EC, Urowitz MB, Gladman DD (1983) Malignancy in progressive systemic sclerosis, association with breast carcinoma. J Rheumatol 10:665–666
10. Masi AT, Rodnan GP, Medsger TA Jr, et al. (1980) Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Arthritis Rheum 23:581–590
11. Scarff RW, Torloni H (1968) Histological typing of breast tumors. International histological classification of tumors, n°2. World Health Organization, Geneva, pp 13–20
12. Talbott JH, Barrocas M (1979) Progressive systemic sclerosis (PSS) and malignancy, pulmonary and non-pulmonary. Medicine (Baltimore) 58:182–207
13. Forbes AM, Woodrow JC, Verbov JL, Graham RM (1989) Carcinoma of breast and scleroderma: four further cases and a literature review. Br J Rheumatol 28:65–69
14. Booton R, Jeffrey R, Prabhu PN (1999) Systemic sclerosis and scleroderma renal crisis in association with carcinoma of the breast. Am J Kidney Dis 34:937–941
15. Darras-Joly C, Wechsler B, Bletry O, Piette JC (1999) De novo systemic sclerosis after radiotherapy: a report of 3 cases. J Rheumatol 22:2265–2267
16. Bleasel NR, Stapleton KM, Commens C, Ahern VA (1999) Radiation-induced localized scleroderma in breast cancer patients. Australas J Dermatol 40:99–102
17. Bielefeld P, Meyer P, Caillot D, et al. (1996) Systemic scleroderma and cancers: 21 cases and review of the literature (in French). Rev Med Interne 17:810–813
18. Hassett C, Harnett P, Manolios N (2001) Scleroderma in association with the use of docetaxel (taxotere) for breast cancer. Clin Exp Rheumatol 19:197–200
19. Davies DA, Cohen PR, McNeese MD, Duvic M (1996) Localized scleroderma in breast cancer patients treated with supervoltage external beam radiation. J Am Acad Dermatol 35:923–927
20. Ross JG, Hussey DH, Mayr NA, Davis CS (1993) Acute and late reactions to radiation in patients with collagen vascular diseases. Cancer 71:3744–3752
21. Hesselstrand R, Scheja A, Akesson A (1998) Mortality and causes of death in a Swedish series of systemic sclerosis patients. Ann Rheum Dis 57:682–686
22. Rattner JB, Rees J, Whitehead CM, et al. (1997) High frequency of neoplasia in patients with autoantibodies to centromere protein CENP-F. Clin Invest Med 20:308–319
23. Kyndt X, Hebbar M, Queyrel V, Hachulla E, Hatron PY, Devulder B (1997) Systemic sclerosis and malignancy: assessment of risk factors associated with the development of cancer in 123 patients with systemic sclerosis. Rev Med Interne 18:1–5
24. Derk CT, Sakkas LI, Rasheed M, Artlett C, Jimenez S (2003) Autoantibodies in patients with systemic sclerosis and cancer: a case-control study. J Rheumatol 30:1994–1996
25. Bevilacqua M, Pober J, Mendrick D, Cotran R, Gimbrone M (1987) Identification of an inducible endothelial-leukocyte adhesion molecule. Proc Natl Acad Sci U S A 84:9238–9242
26. Hebbar M, Lassalle P, Janin A, et al. (1995) E-selectin expression in salivary endothelial cells and sera of patients with systemic sclerosis. Role of resident mast cell-derivated tumor necrosis factor alpha (TNF). Arthritis Rheum 38:406–412

27. Claman H, Giorno RC, Seibold JR (1991) Endothelial and fibroblastic activation in scleroderma. The myth of the ''uninvolved'' skin. Arthritis Rheum 34:1495–1501
28. Zetter B (1993) Adhesion molecules in tumor metastasis. Semin Cancer Biol 4:219–229
29. Recchi MA, Hebbar M, Hornez L, Harduin-Lepers A, Peyrat JP, Delannoy P (1998) Multiplex reverse transcriptase polymerase chain reaction assessment of sialyltransferases expression in human breast cancer. Cancer Res 58:4066–4070
30. Hebbar M, Révillion F, Louchez MM, Fournier C, Bonneterre J, Peyrat JP (1999) Prognostic value of circulating soluble E-Selectin in node-negative breast cancer patients. Clin Cancer Res 5:1427–1435
31. Hebbar M, Révillion F, Louchez MM, et al. (1998) The relationship between concentrations of circulating soluble E-selectin and clinical, biological, and pathological features in patients with breast cancer. Clin Cancer Res 4:373–380
32. Hamada J, Cavanaugh PG, Lotan O (1994) Separable growth and migration factors for large-cell lymphoma cells secreted by microvascular endothelial cells derived from target organs for metastasis. Br J Cancer 66:349–354