Haematological Malignancies in Systemic Sclerosis Patients: Case Reports and Review of the World Literature

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Background. The association of systemic sclerosis (SSc) and haematological cancers was reported in a large number of case reports and cohort studies, describing SSc patients with highly heterogeneous clinical pictures. Objective. We reviewed the literature to better describe SSc patients with haematological malignancies. Methods. SSc cases complicated by haematological malignancies described in the world literature were collected; other 2 cases referred to our centre were reported. Results. One hundred-thirty SSc subjects were collected from 1954 up to date. The mean age of patients at cancer diagnosis was 56.1 ± 16.7 years; 72% of patients were females. In 60% of cases, the diagnosis of haematological malignancy was described within 5 years of SSc diagnosis. In 7.8% of cases, coexistence of Sjögren's syndrome or other autoimmune disorders was cited. Sixty-six cases with lymphoma (in the majority of cases B-cell neoplasms), 28 with leukaemia (chronic lymphocytic form in 9), 14 with multiple myeloma plus one solitary IgM plasmocytoma, and 16 with myeloproliferative disorders were found. No specific SSc subsets seem to be related to haematological malignancies. Conclusions. We remarked the importance of clinical work-up in SSc, in order to early diagnose and treat eventual occult haematological malignancies, especially during the first years of the disease.

1. Introduction

The association between malignancies and connective tissue diseases was widely reported in literature [1]; namely, systemic sclerosis (SSc) has showed relatively high incidence of lung, breast (contrasting data), and haematological cancers, as demonstrated by meta-analysis on population-based cohort studies [2, 3]. However, these studies usually reported the frequencies of specific malignancies in the course of SSc, without further characterization of the patients. In this respect, the subset of “haematological tumours” included different types of malignancies that generally were not described in detail. On the other hand, a large number of case reports may be found in literature [4–54], describing SSc patients with highly heterogeneous clinical pictures complicated by the onset of cancer. These reports could potentially contain detailed data that are not included in registry or large cohort studies [55–67].

The haematological neoplasms originate by the myeloid or the lymphoid cell lines, historically named leukaemias or lymphomas, based on the prevalent location in the blood or the lymph nodes, respectively. Afterwards, more than 70 nosological entities were identified, classified according to the 2008 World Health Organization (WHO) classification of neoplasms of the hematopoietic and lymphoid tissues, on the basis of the recognition of distinctive features in terms of morphology, clinical picture, immunophenotype, and genetic and molecular characteristics [68]. Indeed, the systematic categorization of the haematological malignancies evolved during the decades from the Rappaport classification of 1966 to the WHO classification in 2001 [69], lastly updated in 2016 [70], transposing the new knowledge achieved in the field of histology and cytogenetic/immunohistochemical profiling of malignancies.

In these lights, the known association between SSc and haematological malignancies should be better characterized, especially as regards eventual associations between SSc features and specific type of blood neoplasms. Moreover, specific SSc subsets might be associated with peculiar haematological cancers, besides other comorbid predisposing conditions.
Therefore, we aimed to collect all SSc cases complicated by haematological malignancies described in the world literature, searching eventual specific clinical patterns.

2. Patients and Methods

We analysed the whole SSc patients’ cohort, recruited in our Rheumatology Centre, including 454 cases referred to our university-based hospital from 1 January 2003 to 31 December 2016, in order to find the patients who presented haematological neoplasms in their clinical history, after SSc diagnosis. For all patients, detailed clinical records were available, which eventually comprehended the documentation regarding the haematological diseases.

Secondly, the electronic databases, including PubMed, Embase, Scopus, Web of Science, SciELO, J-Stage, and Google Scholar, were searched for studies that described the cases with the association between haematological cancers and SSc, including all available previous articles and non-English reports. Search terms were “systemic sclerosis” or “scleroderma” and “(a)hematological cancer” or “lymphoma” or “leuk(emi)a”. Myeloproliferative disorders (search terms: “myelofibrosis”, “chronic myelogenous leukaemia”, “polycythemia vera”, “essential thrombocytemia”) were also considered, as well as “MGUS”. All available data included in the published studies were analysed, evaluating all the information useful for patients’ clinical profiling.

We considered all SSc patients who developed blood cancers; otherwise, the cases describing SSc onset after the diagnosis of haematological cancer were excluded. Likewise, the studies that did not exactly indicate the timing of SSc and cancer diagnoses were excluded. On the contrary, the patients with contemporary or very close onset of the two pathologic conditions (blood cancer diagnosis within 1 year from SSc diagnosis) were registered as patients with “probable paraneoplastic” syndrome. Finally, we did not consider studies regarding morphea or localized scleroderma or sclerodermiform syndromes following antineoplastic treatments.

3. Case Reports

3.1. Case 1. A nonsmoker, 35-year-old male patient referred to our centre in 2008 and received a new diagnosis of SSc. The onset of the disease was few months before, featured by skin thickening of face, hands, forearms, and chest; skin ulcers or calcinosis was absent. He complained of Raynaud’s phenomenon, fatigue, and mild sicca syndrome. The disease’s onset dated back to 28 years before. Among SSc features, we emphasize the presence of pulmonary arterial hypertension, treated with sildenafil and, successively, ambrisantan. Calcinosis, telangiectasias, sclerodactyly, and anti-centromere antibodies, but not dysphagia nor interstitial lung disease, were found. As comorbidity, the patient presented severe lower limb arteriopathy obliterans, responsible for digital gangrenous lesions. Moreover, patient’s history was marked by the diagnosis of low-grade tubular breast carcinoma in 2006; then, she underwent right quadrantectomy. Six years later, X-ray scan revealed a 2 cm pulmonary opacity in the right lower lobe. After chest CT confirmation, lobectomy was performed; the histological analysis diagnosed an extranodal marginal mature B cell lymphoma (BALToma). Given the absence of metastasis, no radio-/chemotherapy was considered necessary after the lung resection. To date, the patient is doing well, without presenting recidivism.

3.2. Case 2. A 72-year-old woman referred to our centre in 2012 from another hospital, where she was followed for SSc. The disease’s onset dated back to 28 years before. Among SSc features, we emphasize the presence of pulmonary arterial hypertension, treated with sildenafil and, successively, ambrisantan. Calcinosis, telangiectasias, sclerodactyly, and anti-centromere antibodies, but not dysphagia nor interstitial lung disease, were found. As comorbidity, the patient presented severe lower limb arteriopathy obliterans, responsible for digital gangrenous lesions. Moreover, patient’s history was marked by the diagnosis of low-grade tubular breast carcinoma in 2006; then, she underwent right quadrantectomy. Six years later, X-ray scan revealed a 2 cm pulmonary opacity in the right lower lobe. After chest CT confirmation, lobectomy was performed; the histological analysis diagnosed an extranodal marginal mature B cell lymphoma (BALToma). Given the absence of metastasis, no radio-/chemotherapy was considered necessary after the lung resection. To date, the patient is doing well, without presenting recidivism.

4. Review of the Literature

Table 1 summarized all cases of SSc patients complicated by haematological malignancies found in literature [4–67]; the studies that do not give any information about SSc features and/or haematological cancer types were excluded. Both case reports and cohort studies were included, even though, usually, only the first ones reported complete description of the clinical histories. To the best of our knowledge, 130 (including our 2 cases) subjects affected by SSc and haematological cancer were collected, from the first case described in 1954 up to date. Majority of patients were from Europe and USA and were Caucasian, while 18% of persons were of Asian ethnicity, coming from the Far Eastern Countries. The mean age of patients was 56.1±16.7 years, without gender difference as regards age, with the higher prevalence of cases in the sixth decade. 72% of the cases were women. The diagnosis of haematological malignancies was frequently close to SSc diagnosis: indeed, in about 30% of cases, scleroderma could be considered as “probable paraneoplastic,” while for other 30% of patients the cancer was diagnosed within 5 years of SSc.
diagnosis. Sporadic observations of blood cancer were also reported during the further years, even after several decades.

Among SSc patients with haematological malignancies, the diffuse skin subset was reported in 28% of cases. As regards serology, anticentromere and anti-Scl70 autoantibodies were equally found; of note, a relevant percentage (29%) of specific anti-nuclear autoantibodies (ANA) was observed. Organ SSc involvement was not frequently described; anyway, no peculiar associations may be found, because the malignancies could be observed both in SSc patients with diffuse skin involvement and interstitial lung disease and in the “CREST” patients’ subset. In a few cases, overlapping Sjögren’s syndrome (a disease with well-known increase of haematological cancer risk) was suspected or clearly reported; moreover, rheumatoid arthritis was recognized in 2 patients, porphyria cutanea tarda in other 2, and pemphigus vulgaris in 1. Finally, only in few patients a detailed clinical history was available, giving the possibility of identifying other eventual cancer risk factors (i.e., smoking).

As regards haematological malignancies, we collected 66 cases with lymphoma (including our 2 cases), 28 with leukaemia, 14 with multiple myeloma (plus one solitary IgM plasmocytoma), and 16 with myeloproliferative disorders; in 3 the exact diagnosis was not expressed. Many types of lymphoma were reported, often not better specified than the mere definition of “non-Hodgkin lymphoma”; in the other cases, the diffuse large B cells lymphoma was the most frequent (8 cases plus 1, our case). With the exception of few patients, all lymphomas described are classifiable as mature B cells neoplasms; in fact, we registered only 3 lymphomas of T cells and 2 from histiocytic cells, while 6 cases of Hodgkin’s lymphoma were found.

Considering the 28 cases developing leukaemia, 9 patients showed the chronic lymphocytic form. T cells leukaemia was present in only 2 persons; 8 cases were not better specified. Finally, among myeloproliferative disorders, 4 cases of myelofibrosis and 11 of chronic myelogenous leukaemia were found; just one patient presented polycythemia vera, while no cases of essential thrombocythemia were found.

The clinical courses of the treated patients may be divided into 2 prognostic patterns, substantially equivalent in percentage: (1) rapid improvement up to remission, often associated with SSc features amelioration; (2) rapid deterioration until death from infectious causes. The latter pattern was invariably observed in patients over 50 of age; no other clinical features useful for prognostic purposes were found.

5. Discussion

It is known from the literature that the incidence of haematological malignancies is significantly increased in SSc [1–3]; in this review, we tried to better define this statistical association gathering together all SSc cases complicated by blood cancers previously described. We found that the majority of cases presented the B cells non-Hodgkin lymphoma (especially the diffuse large B cells lymphoma, as well as our case number 1), the multiple myeloma, and the chronic lymphocytic leukaemia; furthermore, also myeloproliferative disorders were frequently described in the course of SSc.
Table 1: Haematological diseases in course of systemic sclerosis.

| First author/year       | Number cases | Study type (country) | Age/sex | Dis. duration | Skin subset | Serology | Visceral inv. | Ass. Sjogren | History notes | Clinical picture | Hematological malignancy | Outcomes |
|-------------------------|--------------|----------------------|---------|---------------|-------------|----------|--------------|--------------|---------------|----------------------|--------------------------|----------|
| Agard/2000              | 1            | CR (France)          | 62 F    | L             | ACA         | None     | No           | MGUS         | Spleno/lymphadenop., ascites | Small B cell NHL           | Improved with CHOP |
| Airoi/2011              | 1            | CS (360 Italian pts) | nd      | nd            | nd          | ACA      | nd           | nd           | None          | NHL                 | nd                      |          |
| Alacacioglu/2005        | 1            | CR (Turkey)          | 57 M    | 3             | nd          | nd       | nd           | nd           | Bilateral upper/lower eyelid hemias | Orbital marginal zone NHL | Improved with chemo/radiation therapy |
| Angeli/1991             | 1            | CR (France)          | 42 F    | 4             | L           | ACA      | nd           | No           | Splenomegaly  | CLL                 | nd                      |          |
| Arai/2009               | 1            | CR (Japan)           | 31 F    | 1             | nd          | nd       | nd           | nd           | None          | Thymic large B-NHL | Remission with CHOP |
| Arnaud/2006             | 1            | CR (France)          | 76 F    | II            | L           | nd       | E            | nd           | H. pylori +   | Gastric MALT lymphoma | nd                      |          |
| Bachleitner-Hofmann/2002| 1            | CR (Austria)         | 73 F    | L             | ACA         | L, E     | nd           | MGUS         | nd            | MM                  | Marked and sustained improvement for MM and SSc |
| Baldini/1994            | 1            | CR (Italy)           | 59 F    | 1             | nd          | ANA      | nd           | nd           | Right axillary lymphadenopathy | CD30+ anaplastic Ly | Lympohoma and SSc remission with BMT |
| Bellis/2014             | 1            | CR (France)          | 37 M    | 1             | L           | ANA      | nd           | nd           | nd            | NHL                 | nd                      |          |
| Ben Ghorbel/2005        | 1            | CR (Turky)           | 70 F    | 6             | L           | Scl70     | L            | No           | Generalized lymphadenopaties | Follicular B NHL | Improved with CHOP |
| Bielefeld/1996          | 5            | CS (21 French pts)   | 39 F, 56 F, 69 F, 12 M, 71 M | 0, 6, 6, 9, 2 | nd          | nd       | nd           | nd           | CML, AML, immunocytoma, Burkitt’s Lymphoma, Waldenstrom d. | nd                      |          |
| Bistue/1990             | 1            | CR (Argentina)       | 36 F    | nd            | D           | nd       | L            | No           | Dyspnea, splenomegaly, and fever | Myelofibrosis | nd                      |
| Cavallero/1994          | 1            | CR (Italy)           | 79 M    | nd            | D           | ANA      | nd           | nd           | Carpenter      | Purpura of legs   | Hairy cell leukemia | Died for pneumonia after 3 months |
| Charlanne/2004          | 1            | CR (France)          | 72 F    | <1            | L           | ACA      | No           | Yes          | Overlap RA-SS  | Neutropenia and lymphocytosis | Large granular lymphocyte leukemia | Sustained (>1 year) improvement with MTX 25/week for leukemia and autoimmunity |
| Chatterjeee/2005        | 5            | RS (538 US pts)      | 2 NHL are F | nd          | 2 NHL:1 LL, 1 D | nd | nd       | nd           | nd            | NHL (2); MM (2); leukemia (1) | nd                      |          |
| Colovic/2011            | 1            | CR (Serbia)          | 55 F    | 20            | L           | nd       | nd           | nd           | Intense facial pruritus, paraproteinemia | MM                  | Remission for SSc and MM |
| Comer/1992              | 1            | CR (UK)              | 31 F    | 1             | L           | ANA      | E, L, H     | No           | Neck/mediastinum lymphadenopathy | 1B-staged HL | HL remission (MOPP), SSc evolution by 1 year |
| Constans/1993           | 1            | CR (France)          | 65 F    | 0             | L           | ACA      | CREST       | No           | Hairy cell leukemia | nd                      |          |
| Derk/2003               | 1            | CR (USA)             | 66 M    | 2             | D           | Scl70     | E            | No           | Expanding mass at the tongue base | Large B-NHL | Remission with CHOP |
| Doyle/1985              | 5            | CS (USA)             | 10; 22; 31 54; 70 F | 4; 9; 9; 40; 57 | L           | nd       | CREST       | nd           | nd            | HL; MM (2); "malignant Lymph"; CLL | Variable outcomes |          |
| First author/year | Number cases | Study type (country) | Age/sex | Dis. duration | Skin subset | Serology | Visceral inv. | Ass. Sjogren | History notes | Clinical picture | Hematological malignancy | Outcomes |
|-------------------|--------------|----------------------|---------|---------------|-------------|----------|--------------|--------------|---------------|----------------|----------------------|----------|
| Duggal/2002       | 1            | CR (India)           | 42 M    | nd            | nd          | nd       | nd           | nd           | nd            | nd            | HL                   | nd       |
| Duncan/1979       | 7            | CS (2,141 USA pts)   | 50–79 F | 2, 0, 1, 3, 0, 0, 1, 1 | nd          | nd       | nd           | nd           | nd            | nd            | CLL (3), MM, lymphosarcoma (2), CMML | Died by 1 year (2), alive > 5 years (4) |
| Dupond/1989       | 1            | CR (France)          | 73 F    | nd            | L           | ACA      | CREST, L    | Yes          | nd            | Splenomegaly    | nd                   | Diagnosis at autopsy | nd       |
| Ferroir/1991      | 1            | CR (France)          | 42 M    | 2            | nd          | ANA      | nd           | No           | nd            | nd            | Mixed follicular Ly | nd       |
| Frigui            | 1            | CR (France)          | 56 F    | 10           | L           | Scl70    | L, K        | No           | nd            | Skin lesion     | Cutaneous B-cell Ly (supraorbital) | Regression after radiotherapy but relapse | nd       |
| Gisser/1979       | 1            | CR (USA)             | 29 F    | 4            | nd          | nd       | L, H        | nd           | Previous chlorambucil treat. | Anemia | CML                   | Died for bronchopneumonia | nd       |
| Hall/1978         | 1            | CR (USA)             | 22 F    | 14           | nd          | nd       | E calcinosis | No           | Generalized lipodystrophy | Diffuse lymphoproliferations | Nodular sclerosing HL | nd       |
| Hasegawa/1999     | 1            | CR (Japan)           | 43 M    | <1           | D           | ANoA     | nd           | No           | nd            | Neck/axillar lymphoproliferations | Diffuse large T cell NHL | Lymphoma and SSc remission (CHOP 4 cycles) | nd       |
| Haviv/1997        | 1            | CR (Israel)          | 72 F    | 1, 5         | L           | ANA      | L, K        | No           | Fever, wasting, and arthralgias | Diffuse small cell NHL | Death for sepsis | nd       |
| Hill/2003         | 2            | RS (441 Australian pts) | F   | nd            | nd          | nd       | nd           | nd           | nd            | nd            | Neutrophilic.omal NHL | Not better specified | nd       |
| Hoshida/2004      | 7            | CS (Japan)           | 57 (56–65), 2/5 M/F | 2.2 (0–12) | nd          | nd       | nd           | 2/7          | nd            | HL (2), diffuse large B cell Ly (5) | All died by 1 year | nd       |
| Kaşifoğlu/2006    | 1            | CR (Turkey)          | 50 F    | 7            | L           | Scl70    | L           | SSA+         | Weakness, weight loss | CML | Improved with HU | nd       |
| Kaşifoğlu/2016    | 3            | CS (340 Turkish pts) | nd      | nd            | nd          | nd       | nd           | nd           | MM, CML, follicular NHL | nd       |
| Katz/1979         | 1            | CR (USA)             | 57      | 11           | nd          | ANA      | nd           | nd           | Pemphigus v. | Diffuse histiocytic Ly | nd       |
| Kyndt/1997        | 1            | CS (123 French pts)  | 76 F    | 8            | nd          | Scl70    | L           | Yes          | nd            | nd            | CMML                 | nd       |
| Kojima/2006       | 2            | CS (Japan)           | nd      | nd            | nd          | nd       | nd           | nd           | nd            | nd            | B cell follicular Ly | nd       |
| Kuo/2012          | 6            | RS (2,053 Taiwanese pts) | 1 M, 5 F | nd            | nd          | nd       | nd           | nd           | nd            | nd            | Ly (3), myeloprolif. dis. (2), CML (2) | nd       |
| Lee/2001          | 1            | CR (Korea)           | 56 F    | 15           | L           | ACA      | CREST       | No           | Porphyria c.t. | Splenomegaly     | Myelofibrosis         | nd       |
| Marto/2014        | 1            | CR (Portugal)        | 76 F    | 0            | L           | ACA      | L           | No           | Multiple polyps of the colon | Multiple adenocarcinoma, diarrhea, and rectorrhagia | IIb-staged mantle cell NHL of the colon | Ly remission with R-CHOP | nd       |
| Miyamoto/2000     | 1            | CR (Japan)           | 55 F    | 17           | nd          | nd       | nd           | No           | Fever, fatigue, pancytopenia, and splenomegaly | Myelofibrosis | Treated with pulse steroids and transfusions | nd       |
| Olesen/2010       | 18           | RS (2,040 Danish pts) | M/F 9/9 | 2/18 :<1     | nd          | nd       | nd           | nd           | nd            | nd            | NHL (10); leukaemia (7) | nd       |
| First author/year                      | Number cases | Study type (country) | Age/sex | Dis. duration | Skin subset | Serology | Visceral inv. | Ass. Sjogren | History notes                  | Clinical picture                                      | Hematological malignancy | Outcomes                                      |
|----------------------------------------|--------------|----------------------|---------|---------------|-------------|----------|--------------|-------------|---------------------------------|------------------------------------------------------|--------------------------|---------------------------------------------|
| Owlia/2014                             | 1            | CR (Iran)            | 58 M    | 15            | L           | nd       | E            | No          | smoker (30 p-y)                  | Lumbar pain (extensive bony infiltration)            | MM                       | Death 2 years after VAD/bortezomib         |
| Ozturk/2006                            | 1            | CR (Turkey)          | 54 F    | 5             | L           | nd       | CREST        | No          | nd                              | Sweet syndrome                                      | Myelofibrosis             | Improved with steroids and hydroxyurea       |
| Parma/1996                             | 1            | CR (Italy)           | 68      | 3             | nd          | nd       | nd           | nd          | Primitive muscle and bone involv.| Large multilobated B-cell NHL                      | Improved                 |                                              |
| Prochorec-Sobieszek/2004                | 1            | CR (Poland)          | 22 F    | <1            | L           | PmScl     | No           | nd          | Parotid swelling                 | Parotid MALToma                                       | nd                       |                                              |
| Rodrigues/1989                         | 1            | CR (Brazil)          |          |               | nd          | nd       | nd           | nd          | Concom. thyroid adenoca.         | Ileal B-cell Ly                                   | Rapid deterioration until death                   |
| Rosenthal/1993                         | 3            | RS (233 Swedish pts) |          | <1 (1)        | nd          | nd       | nd           | nd          | nd                              | NHL (2), not better specified hematological cancer (1)| nd                       |                                              |
| Rothfield/1992                         | 1            | CS (148 USA pts)     |          |               | nd          | nd       | nd           | nd          | Scl70                           | Lymphocytic Ly                                       | nd                       |                                              |
| Roumm/1985                             | 3            | CS (262 USA pts)     | 33 F, 50 F; 71 F | nd | 3.5, 6.5, 5.5 | nd         | nd           | nd          | nd                              | CML, AML, and histiocytic Ly                         | nd                       |                                              |
| Ryczek/2013                            | 1            | CR (Poland)          |          |               | nd          | nd       | nd           | nd          | nd                              | CML                                                  | nd                       |                                              |
| Schnack/1954                           | 1            | CR (Austria)         | 53 F    | 8             | D           | nd       | nd           | nd          | nd                              | MM                                                   | nd                       |                                              |
| Senel/2006                             | 1            | CR (Turkey)          | 65 F    | 0             | D           | Scl70     | L, K        | No          | nd                              | Weakness, sweating, and weight loss                 | CML                      |                                              |
| Shvidel/2002                           | 1            | CS (Israel)          | 71 F    |               | nd          | nd       | nd           | nd          | nd                              | MM (2), diffuse large B-NHL, thyroid NHL, solitary IgM PC | nd                       |                                              |
| Siau/2011                              | 5            | CS (68 UK pts)       | 0 (case of PC) | L | nd           | nd         | nd           | nd          | nd                              | Generalized lympho adenopathy                        | B-CLL                    | Alive up to 2 years; death for bronchopneumonia and paralytic ileus |
| Sidi/1990                              | 2            | CS (Israel)          | 47 M, 77 M | 20; 11      | L           | nd       | CREST        | No          | nd                              | Generalized lympho adenopathy                        | B-CLL                    | Death after 3 COPP cycles for complicating interstitial pneumonitis |
| Sugai/1987                             | 1            | CR (Japan)           | 67 F    | II            | D           | ANA       | E, L        | Yes         | nd                              | Parotid swelling and generalized lymphadenopathy     | IIb-staged NHL                        | Death for pneumonitis during BACOPP chemotherapy |
| Suzuki/1994                            | 1            | CR (Japan)           | 68 M    | 3             | D           | ANA       | nd          | No          | nd                              | Gait disturbance, anemia, and hemorrhagic stroke     | Brain diffuse large B-NHL | Death for pneumonitis during BACOPP chemotherapy |
| Szekanecz/2008                         | 3            | CS (218 Hungarian pts) | 53; 67; 69 F | 2.19; 0.7 | D           | Scl70; L-H-E; none; L-H-K-E | nd | nd          | nd                              | (2) b-CLL; (1) chronic small lymphocytic B NHL       | Surviving > 5 years           |                                              |
| First author/year | Number cases | Study type (country) | Age/sex | Dis. duration | Skin subset | Serology | Visceral invol. | Ass. Sjogren | History notes | Clinical picture | Hematological malignancy | Outcomes |
|-------------------|--------------|----------------------|---------|---------------|-------------|----------|---------------|-------------|---------------|----------------|------------------------|----------|
| Talbott/1979      | 2            | CS (USA)             | 64 M; 73 F | <; 10         | L; D        | nd       | None; L-H   | Probable    | Pt number 1 coal miner | Backache; generalized weakness | MM       | Rapid deterioration and death |
| Vettori/2010      | 1            | CR (Italy)           | 45 F    | nd            | nd         | nd       | nd           | nd          | Leukocytosis, thrombocytosis | Progressive weight loss | Gastric B-cell Ly | CML remission and SSc improvement with therapy |
| Watanabe/1994     | 1            | CR (Japan)           | 44 F    | nd            | nd         | nd       | nd           | nd          | Leukocytosis, thrombocytosis | CML       | CML remission and SSc improvement with therapy |
| Williams/2011     | 1            | CR (USA)             | 61 M    | 30            | L          | ACA      | E, L        | No          | Thrombocytopenia, cervical adenopathy | Small lymphocytic B-NHL | Remission with PCR |
| Wooten/1998       | 1            | CR (USA)             | nd      | 3             | L          | CREST    | nd           | Porphyria c.t. | nd            | CML       | Died 6 months after CHOP therapy because of sepsis, initially improved |
| Yamamoto/2005     | 1            | CR (Japan)           | 72 M    | 5             | D          | Scl70    | L           | nd          | Multiple lymphadenopathy | Angioimmunobl. T cell Ly with EBV-assoc. B cell lymphoprol. dis. | Died 6 months after CHOP therapy because of sepsis, initially improved |
| Present study     | 2            | CR (Italy)           | 37 M; 72 F | 2; 28         | SSA/SSB    | ACA      | E; L        | CREST + L   | Yes; no previous breast cancer | Weakness, sweating, and weight loss; asymptomatic | Diffuse large B-NHL: marginal B-NHL | Died few months after CHOP therapy; lung lobe resection and remission |

Total 130 pts

The table included all the case reports and the cohort studies that reported cases of haematological malignancies in the course of SSc [4–67]. Pts = patients; type of study: CR = case report; CS = case series/cohort studies; RS = registry studies; skin subset: D = diffuse, L = limited; serology: ACA = anticientromere, Scl70 = anti-topoisomerase I, ANA = specific antinuclear autoantibodies; organ involvements: K = kidney, L = lung, H = heart, E = esophagus; MGUS = monoclonal gammopathy of undetermined significance; CREST = former acronym for limited SSc form including calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia; CML = chronic myelogenous leukemia; AML = acute myelogenous leukemia; MM = multiple myeloma; PC = plasmacytoma; NHL = non-Hodgkin lymphoma; CMML = chronic myelomonocytic leukemia; Ly = lymphoma; HL = Hodgkin lymphoma; MTX = methotrexate; (R-)CHOP = chemotherapeutic regimen for NHL; FCR = chemotherapeutic regimen with fludarabine, cyclophosphamide, and rituximab; BMT = bone marrow transplantation; (BA)COPP = bleomycin, Adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone; MOPP = mustine, vincristine, procarbazine, and prednisone; HU = hydroxyurea; VAD = vincristine, doxorubicin, and dexamethasone.
Besides the heterogeneity of the cases reported in literature, we found that the diagnosis of haematological neoplasms was a precocious event in SSc patients’ clinical histories, particularly within 5 years of SSc diagnosis in the majority of cases (Figure 2). Therefore, given the possibility of successful treatments for a potentially aggressive disease, the clinical-serological surveillance for haematological malignancies in SSc patients should be addressed.

Regarding the demographic characteristics of the SSc patients with blood cancers, we found a higher frequency of males (28%) in comparison to the female/male ratio previously described in large SSc case series [72], probably because of the higher NHL incidence among male subjects [73].

Even though anecdotal in several patients, we underline the coexistence of other autoimmune disorders or pathologic conditions known for their increased risk of cancer. Indeed, the omission of relevant anamnestic information in the descriptions of patients reported in literature is presumable, especially for the registry/large cohort-based studies designed for the statistical analysis of cancers epidemiology. As regards serology, the presence of a specific ANA in SSc patients with haematological cancers was found in 29% of cases, more than generally reported in previous cohort studies [72], probably because of the higher NHL incidence among male subjects [73].

Even though anecdotal in several patients, we underline the coexistence of other autoimmune disorders or pathologic conditions known for their increased risk of cancer. Indeed, the omission of relevant anamnestic information in the descriptions of patients reported in literature is presumable, especially for the registry/large cohort-based studies designed for the statistical analysis of cancers epidemiology. As regards serology, the presence of a specific ANA in SSc patients with haematological cancers was found in 29% of cases, more than generally reported in previous cohort studies [72], probably because of the higher NHL incidence among male subjects [73]. In this respect, Altintas et al. [74] detected ANA in more than 20% of 179 patients affected by lymphomas, even though the majority of them did not show autoimmune diseases. Furthermore, in an elegant study by Guyomard et al. [75], 347 NHL patients and 213 controls were investigated by means of indirect immunofluorescence technique on Hep2 cells. ANA were significantly more frequent in the first group (19% versus 5.6%), before any treatment, particularly in presence of follicular or mantle B cell lymphomas. The latter are characterized by a high rate of cells proliferation and a large number of apoptotic cells, leading to the exposition of large amount of nuclear antigens, eventually targeted by patients’ immune system.

The association between autoimmune diseases and haematological neoplasms is an intriguing question; indeed, more than 10% of lymphoid malignancies occur in the setting of an autoimmune disorder [76]. Accumulated evidences indicate that autoreactive B cells are more prone to undergo malignant transformation. In parallel, the chronic activation of the inflammatory response due to autoantigen-driven immune stimulation in specific organ tissues (i.e., the parotid gland in Sjögren's syndrome) is associated with an increased risk of lymphomas [76,77]. Furthermore, the epidemiological data from large population studies on other autoimmune diseases, such as rheumatoid arthritis or systemic lupus erythematosus, showed a high risk of B cells haematological neoplasms, particularly the diffuse large B cell lymphoma [78,79]. Consistently, in SSc, we found a clear-cut prevalence of B cells versus the T cells cancers, suggesting that the systemic autoimmune activation plays a pivotal role in the carcinogenic evolution.

Besides the evidences of pathogenetic and statistical links between SSc and haematological malignancies [1–3], the exact mechanism responsible for cancers is not understood. In other autoimmune disorders specific etiologic factors (i.e., HCV for mixed cryoglobulinemia [80]) lead to persistent stimulation of the immune system and, eventually, to lymphomagenesis. Differently, SSc etiology remains obscure, despite the probable role of a few infectious triggers able to chronically infect immune cells [81]. Overall, a deeper knowledge of the SSc etiopathogenetic processes, probably different for several disease’s subsets, could help to better quantify the risk for different types of cancers, including haematological neoplasms.

Since the majority of patients described in the present study developed the tumours in the first years of the disease (Figure 2), including our first case, the possible iatrogenic effect of immunosuppressors may be easily excluded. On the contrary, it was hypothesized that the immune alterations in the early phase of SSc present a different pattern, which tends to change during the disease’s follow-up [82].

We previously demonstrated a high prevalence of thymic hyperplasia in SSc patients, particularly during the first years of the disease [71]. Given the fundamental role of the thymus in the maturation of T lymphocytes, it might be assumed that a pathological alteration of the thymic microenvironment could lead to a deficient or incomplete T cell maturation, which might have a role in the immunological alterations of SSc etiopathogenesis. Nonetheless, the autoreactivity of T cells strictly involves also B cells that produce a number of
different autoantibodies, which in turn stimulate fibroblasts’
toll-like receptors-4 [83] and induce endothelial dysfunction
[84]. B cell infiltrates may be detected in SSc patients’ skin
or in affected areas of the lungs, so giving the rationale for
the therapeutic use of rituximab [85]. Therefore, even though
T cells are considered the driving force of the autoimmune
pathogenesis in SSc, it is not surprisingly the observation of
an increased risk for B cells-derived malignancies.

Upon the onset of autoimmune responses, lymphoid
tissues undergo histological changes due to the remodelling
of the tissue architecture in parallel with the phenotypic
transformations of immune cell populations. Recently, San-
galetti et al. [76] hypothesized that an erroneous remodelling
of the stromal microenvironment in secondary lymphoid
organs could facilitate malignant transformation of lympho-
cytes, in presence of persistent immune stimulation. Thus,
lymphomagenesis would be a result of disrupted myeloid
and lymphoid function in lymphoid tissues that harbour
autoreactive proliferating T and B cells. In this respect, our
paradigmatic case developed a lymphoma that probably rose
in the thymus, which was histologically disrupted by the
preexistent thymic hyperplasia.

In SSc patients, several studies demonstrated the activa-
tion status of the peripheral B lymphocytes with an impaired
percentage of apoptotic cells compared to healthy controls
[86]. Moreover, Wang et al. [87] found that the levels of his-
tone acetylation and methylation (responsible for increased
gene transcription) in B cells from SSc patients correlate with
disease activity. Furthermore, serum concentrations of BAFF
and APRIL, cytokines regulating B cell activity, survival,
and proliferation, are found elevated in SSc in comparison
with healthy controls, particularly in patients with active
or severe disease [86]. In this light, we might assume that
the sclerodermic patients with poorly controlled disease (an
occurrence more probable in the early phase of SSc, like
in our first case) are more prone to develop haematological
malignancies in their clinical histories.

In SSc, the increase of B cells survival and activation
sounds apparently in contrast with the finding of augmented
Fas (CD95) expression on the surface of memory B cell that
facilitate Fas-mediated apoptosis. However, the incessant loss
of these lymphocytes is coupled to the increased production
of naive B cells and plasma cells in order to maintain B
cell homeostasis [88]. Therefore, the amplification of the
percentage of less mature B lymphocytes understandably
leads to a major risk for lymphoid carcinogenesis.

Finally, as opposite scenario, we briefly mention the
possibility that cancer mutations might trigger SSc itself, at
least in patients with anti-RNA polymerase III autoantibodies
[89]. Neoplasms could harbour missense mutations in the
gene coding for the polymerase III polypeptide A, leading to
the production of an altered protein. The latter could
stimulate an immune response and, possibly, a cross-reaction
against the normal protein; this immune response could be
relevant in the pathogenesis of a subset of SSc [90].

The present study shows a few limitations. Firstly, even
though this review included the higher possible number of
studies, several cases of SSc complicated by blood cancers
described in literature were lost [91, 92], because of the
unavailability of the necessary information for the purposes
of our study. This limitation may be exceeded only with
further studies designed ad hoc, including large case series.

Secondly, our review included a number of case reports,
in which contemporaneous SSc and haematological malign-
ancy are more likely to be reported than cases where
the diagnoses are far apart. In particular, SSc patients who
suffered from haematological malignancies longer after SSc
onset were more unlikely to be published because it was
difficult to emphasize the relationship of ‘SSc and haema-
tological malignancies’. However, also SSc cohort studies
seem to confirm the higher incidence of blood cancers
in the first years of SSc. Anyway, the eventual exposure
to immnosuppressive therapy in SSc patients with longer
disease duration could be considered a further risk factor for
cancer development.

In conclusion, SSc may be complicated by several types
of cancers, including haematological malignancies. More
frequently, B cells-derived lymphomas and leukaemias may
be diagnosed in the first years of the disease and represent
a significant warning for patients’ prognosis. To date, no
specific SSc features could predict which subjects present
major risk for blood cancer; thus, a careful surveillance of SSc
patients should be addressed.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

[1] N. Zeineddine, L. E. Khoury, and J. Mosak, “Systemic sclerosis
and malignancy: a review of current data,” Journal of Clinical
Medicine Research, vol. 8, pp. 625–632, 2016.

[2] A. Onishi, D. Sugiyama, S. Kumagai, and A. Morinobu, “Cancer
incidence in systemic sclerosis: meta-analysis of population-
based cohort studies,” Arthritis and Rheumatism, vol. 65, no. 7,
1913–1921, 2013.

[3] M. Bonifazi, I. Tramacere, G. Pomponio et al., “Systemic
sclerosis (scleroderma) and cancer risk: systematic review and
meta-analysis of observational studies,” Rheumatology, vol. 52,
Article ID kes303, pp. 143–154, 2013.

[4] C. Agard, T. Ponge, B. Mahé, and I. Barrier, “Lymphocytic lymph-
oma and regenerative liver nodular hyperplasia in systemic scleroderma,” La Revue de Médecine Interne, vol. 21, pp. 301–
303, 2000.

[5] I. Alacacioglu, M. A. Ozcan, N. Kocak et al., “Bilateral primary orbital non-Hodgkin’s lymphoma in a patient with scleroderma: a case report,” Leukemia and Lymphoma, vol. 46, no. 8, pp. 1239–
1242, 2005.

[6] C. Angelii, J. P. Lacour, B. Taillan, and J. P. Ortonne, “Chronic
lymphoid leukemia in a case of scleroderma,” in Presse Med, vol.
20, p. 426, 1991.

[7] H. Arai, H. Iso, Y. Arai et al., “Mediastinal large B-cell lymphoma associated with systemic sclerosis,” in Joint Bone Spine, vol. 73, no. 1,
pp. 105–108, 2006.
lymphoma (MALI) of salivary glands and scleroderma: a case report,” *Clinical Rheumatology*, vol. 23, no. 4, pp. 348–350, 2004.

[41] C. J. Rodrigues, H. Bisi, N. Yoshinari, P. E. Marchiori, and W. Cossermelli, “Progressive sclerosis, B-cell malignant lymphoma of the ileum and thyroid adenocarcinoma,” *Rev Hosp Clin Fac Med Sao Paulo*, vol. 44, pp. 84–86, 1989.

[42] R. Ryczek, J. Góra-Tybor, K. Betkier-Lipińska, and A. Cwetsch, “Reversible pulmonary hypertension as a consequence of dasta-tinib treatment in a patient with chronic myeloid leukemia and scleroderma,” *Polski Merkuriusz Lekarski: Organ Polskiego Towarzystwa Lekarskiego*, vol. 34, pp. 342–344, 2013.

[43] H. Schnack and N. Stefanello, “A case of diffuse generalized scleroderma and plasmocytoma,” *Wien Klin Wochenschr*, vol. 66, pp. 862–864, 1954.

[44] S. Senel, E. Kay, I. Aydogdu, M. A. Erkurt, and I. Kuku, “Rheumatic diseases and chronic myelogenous leukemia, presentation of four cases and review of the literature,” *Rheumatology International*, vol. 26, no. 9, pp. 857–861, 2006.

[45] L. Shvidel, C. Duksin, A. Tzimanis et al., “Cytokine release by activated T-cells in large granular lymphocytic leukemia associated with autoimmune disorders,” *The Hematology Journal*, vol. 3, pp. 32–37, 2002.

[46] Y. Sidi, R. Fadilah, J. Pinkhas, and M. Prokocimer, “Systemic sclerosis and chronic lymphocytic leukaemia,” *Postgraduate Medical Journal*, vol. 66, no. 782, pp. 1071–1072, 1990.

[47] S. Sugai, J. Tachibana, M. Sawada et al., “Malignant lymphomas in patients with autoimmune diseases: a report of 6 cases and a review of the Japanese literature,” *Japanese Journal of Medicine*, vol. 26, no. 3, pp. 339–347, 1987.

[48] A. Suzuki, H. Ohoike, Y. Kitagawa, Y. Matsuoka, and S. Irimajiri, “Progressive systemic sclerosis complicated with primary cerebral malignant lymphoma,” *Internal Medicine*, vol. 33, no. 9, pp. 557–559, 1994.

[49] J. H. Talbott and M. Barrocas, “Progressive systemic sclerosis (PSS) and malignancy, pulmonary and non-pulmonary,” *Medicine*, vol. 58, pp. 182–207, 1979.

[50] S. Vettori, S. Staibano, M. Mascolo, G. Ilardi, and G. Valentini, “Non-Hodgkin's lymphoma in systemic sclerosis: case and literature review,” *Clinical Rheumatology*, vol. 29, no. 1, pp. 1–6, 2010.

[51] S. Watanabe, T. Sugihara, M. Takahashi et al., “Concordant improvement of progressive systemic sclerosis and chronic myelogenous leukemia with interferon-alpha treatment,” *Rinsho Ketsuiki*, vol. 35, pp. 895–897, 1994.

[52] B. M. William, T. Harbert, A. K. Ganti, and P. J. Bierman, “Small lymphocytic lymphoma in a patient with CREST syndrome,” *Hematology Oncology and Stem Cell Therapy*, vol. 4, no. 3, pp. 132–135, 2011.

[53] M. D. Wooten, J. W. Scott, A. M. Miller, and E. Boh, “Chronic myelogenous leukemia and porphyria cutanea tarda in a patient with limited systemic sclerosis,” *Southern Medical Journal*, vol. 91, no. 5, pp. 493–495, 1998.

[54] H. Yamamoto, H. Miwa, Y. Kato, S. Nakamura, K. Hara, and M. Nitta, “Angioimmunoblastic T cell lymphoma with an unusual proliferation of Epstein-Barr virus-associated large B cells arising in a patient with progressive systemic sclerosis,” *Acta Haematologica*, vol. 114, no. 2, pp. 108–112, 2005.

[55] P. Airo, A. Ceribelli, I. Cavadonna, M. Taraborelli, S. Zingarelli, and F. Franceschini, “Malignancies in Italian patients with systemic sclerosis positive for anti-RNA polymerase III antibodies,” *The Journal of Rheumatology*, vol. 38, no. 7, pp. 1329–1334, 2011.
A. Altintas, T. Cil, S. Pasa, and et, "Clinical significance of elevated antinuclear antibody test in patients with hodgkin's and non-hodgkin's lymphoma: a single center experience," Minerva Medica, vol. 99, pp. 7–14, 2008.

S. Guyomard, G. Salles, M. Coudurier et al., "Prevalence and pattern of antinuclear autoantibodies in 347 patients with non-Hodgkin's lymphoma," British Journal of Haematology, vol. 123, no. 1, pp. 90–99, 2003.

S. Sangaletti, C. Tripodo, C. Vitali et al., "Defective stromal remodelling and neutrophil extracellular traps in lymphoid tissues favor the transition from autoimmunity to lymphoma," Cancer Discovery, vol. 4, no. 1, pp. 110–129, 2014.

K. E. Smedby, H. Hjalgrim, J. Askling et al., "Autoimmune and chronic inflammatory disorders and risk of non-Hodgkin lymphoma by subtype," Journal of the National Cancer Institute, vol. 98, no. 1, pp. 51–60, 2006.

A. G. Singh, S. Singh, and E. L. Matteson, "Rate, risk factors and causes of mortality in patients with sjögren's syndrome: a systematic review and meta-analysis of cohort studies," Rheumatology, vol. 55, no. 3, pp. 450–460, 2016.

T. A. Simon, A. Thompson, K. K. Gandhi, M. C. Hochberg, and S. Suissa, "Incidence of malignancy in adult patients with rheumatoid arthritis: a meta-analysis," Arthritis Research & Therapy, vol. 17, Article ID 212, 2015.

C. Ferri, D. Giuggioli, and M. Colaci, "Viral infections and sclerosis," Clin Exp Rheumatol, vol. 32, Supplement 86, no. 6, p. 229, 2014.

C. G. Joseph, E. Darrah, A. A. Shah et al., "Association of the autoimmune disease scleroderma with an immunologic response to cancer," Science, vol. 343, no. 6167, pp. 152–157, 2014.