JSRD Journal of Scleroderma and Related Disorders

Case Report

Extranodal localization of non-Hodgkin's lymphoma in systemic sclerosis: A diagnostic challenge and review of the literature

Journal of Scleroderma and Related Disorders
2022, Vol. 7(3) NP1–NP6

DOI: 10.1177/23971983221088459
journals.sagepub.com/home/jso
SAGE

Giorgio Galoppini[1], Beatrice Maranini[1], Giovanni Ciancio[1], Melissa Padovan[1], Gian Luca Casoni[2], Francesco Cavazzini[3], Roberta Gafà[4], Giovanni Lanza[4] and Marcello Govoni[1]

Abstract

Background: Systemic sclerosis is associated with an increased incidence of malignancies, in particular solid neoplasms. Hematological cancers have been also observed in autoimmune diseases, though rarely present with lung involvement. The latter may be misdiagnosed in systemic sclerosis patients, due to the frequent concomitant interstitial lung disease.
Case description: Here, we present the case of a 63-year-old man affected by systemic sclerosis presenting with an atypical lung imaging and splenomegaly, who was diagnosed with splenic marginal zone lymphoma, thus raising the suspicion of lung secondarism. We discuss the diagnostic challenge of differential diagnosis in interstitial lung presentation and briefly review the available literature on this topic.
Conclusion: Several reports have demonstrated an increased risk of malignancy in patients with systemic sclerosis. Still, the lack of concretely defined guidelines for systemic sclerosis, along with systemic sclerosis multifaceted organ involvement at presentation, may challenge diagnosis and management. Here, we remark the importance of clinical work-up and a multidisciplinary approach in systemic sclerosis, to early detect and treat concomitant hematological malignancies, especially during the first years of the disease.

Keywords

Systemic sclerosis, hematological malignancies, splenic marginal zone lymphoma, B-cell lymphoma

Date received: 16 February 2022; accepted: 1 March 2022

Introduction

Systemic sclerosis (SSc) is a rare multisystemic connective tissue disease (CTD), characterized by immune-mediated microvascular damage leading to fibrosis of involved organs. Skin thickening and hardening are the most prominent features, although patients may have one or more internal organs affected, such as the lungs, heart, kidneys, and gastrointestinal tract. SSc patients have an increased risk of death compared with the general population, and interstitial lung disease (ILD) carries the highest load in terms of morbidity and mortality.[1] Early detection and immunosuppressive therapies have improved the prognosis, although some cases may be unresponsive to conventional treatment and therefore may benefit from investigational treatments.

The association between malignancies and CTDs has been widely reported in the literature.[2] Several reports have demonstrated an increased incidence of malignancy

[1]Rheumatology Unit, Department of Medical Sciences, University of Ferrara, Ferrara, Italy
[2]Pneumology Unit, Hospital of Rovigo, Rovigo, Italy
[3]Hematology Unit, Department of Medical Sciences, University of Ferrara, Ferrara, Italy
[4]Pathology Unit, Department of Medical Sciences, University of Ferrara, Ferrara, Italy

Corresponding author:
Giorgio Galoppini, Rheumatology Unit, Department of Medical Sciences, University of Ferrara, 44121 Ferrara, Italy.
Email: gio.galoppini@gmail.com

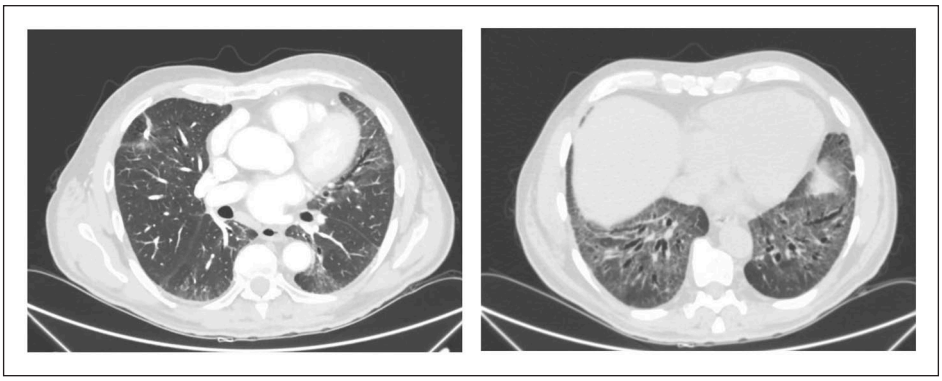

Figure 1. HRCT imaging showing bibasal ground-glass opacities, peribronchial-perivascular fibrosis and bronchiectasias, compatible with NSIP pulmonary fibrosis pattern. Multiple hilar-mediastinal lymphadenomegalies are appreciable (maximum diameter of 26 mm × 9 mm in subcarinal location and approximately 20 mm × 9 mm in right paratracheal location). Two rounded lingular nodules (maximum diameter 6 mm, stable) and a subpleural micronodule of 3 mm diameter in the posterior segment of the upper right pulmonary lobe were both known from the previous HRCT.

in patients with SSc, in particular lung, breast, and hematological cancers.[3–5]

Splenic marginal zone lymphoma (SMZL) is an uncommon, indolent B-cell non-Hodgkin's lymphoma (NHL) derived from mature postgerminal center B lymphocytes. It is usually diagnosed accidentally, although it can present with lymphocytosis, together with systemic symptoms or symptoms related to splenomegaly and/or cytopenias. Some patients may also present signs and symptoms of autoimmune diseases, such as autoimmune hemolytic anemia, immune thrombocytopenia, and antiphospholipid syndrome. Most patients do not require specific management other than close follow-up, although those who progress to large cell transformation are suitable for pharmacological therapy. Rituximab (RTX), a chimeric monoclonal antibody targeting CD20 antigen on B-lymphocyte surface, represents the first-line treatment, alone or in combination with chemotherapy.[6]

Here, we present the case of an SMZL in SSc-associated interstitial lung involvement, suspected to be an extranodal localization of the same hematological neoplasm.

Case description

A 63-year-old male professional bricklayer presented to our Rheumatological clinic in September 2019 with a few months history of acrocyanosis associated with forearms, hands, and chest skin thickening. The patient also reported a weight loss of 15 kg in the past 4 months.

His medical history was also consistent with esophagitis, colic diverticula, multinodular goiter, and hypothyroidism (ongoing substitutive hormonal treatment). He was a nonsmoker and nonalcohol abuser. In March 2019, the patient had undergone surgical removal of a middle lobe pulmonary nodule (discovered with a thoracic high-resolution computed tomography (HRCT) performed to investigate suspicious dyspnea). The nodule turned out an intraparenchymal lymph node with a centrally fibrosclerotic area encompassing anthracitic macrophages and free anthracite pigment; immunoreactivity was positive for CD45, protein S-100, MelanA, and HMB45. Shortly after the patient also underwent videotorachoscopic surgical lysis of pleura-parenchymal synechiae (due to contralateral pleural effusion after surgery); the histopathologic study of bioptic specimens did not reveal mesothelial neoplastic cells, but lymphoid aggregates and fibrosclerotic notes were seen. A diagnosis of pneumoconiosis was made.

On initial examination sclerodactyly, microstomia, palmar, and facial telangiectasias were detected (modified Rodnan Skin Score (mRSS) = 12). Skin ulcers or calcinosis were absent. No inflammatory joint involvement was registered both clinically and ultrasonographically.

Chest auscultation demonstrated reduced air entry over the entire lung lobes, associated with bilateral basal fine crackles. Antinuclear antibodies (ANAs) were screened using enzyme-linked immunosorbent assay (ELISA) and found positive with a title of 1 of 640 speckled patterns. Autoantibodies against extractable nuclear antigens (ENAs) were found positive (8.0 ratio, with a cutoff > 1.0), especially for antitopoisomerase 1 antibodies (Scl-70 > 240 U/mL, positivity cutoff > 10.0). Mild C3 complement component consumption was documented (83 mg/dL, normal range 90–180). Wide microbiologic screening was performed and found negative (among tests, *Mycobacterium tuberculosis*, HBV, HCV, and HIV). Capillaroscopy was then performed, showing aspects consistent with an early-active scleroderma pattern. A diagnosis of systemic sclerosis was then performed.

HRCT documented the presence of interstitial lung disease with nonspecific interstitial pneumonia (NSIP) pattern (Figure 1). At lung function tests, reduction of forced vital capacity (FVC) to 60% and pulmonary diffusion for carbon monoxide (DLCO) to 38% were registered. Cardiac function was normal, and no signs of pulmonary hypertension were found at heart ultrasonography.

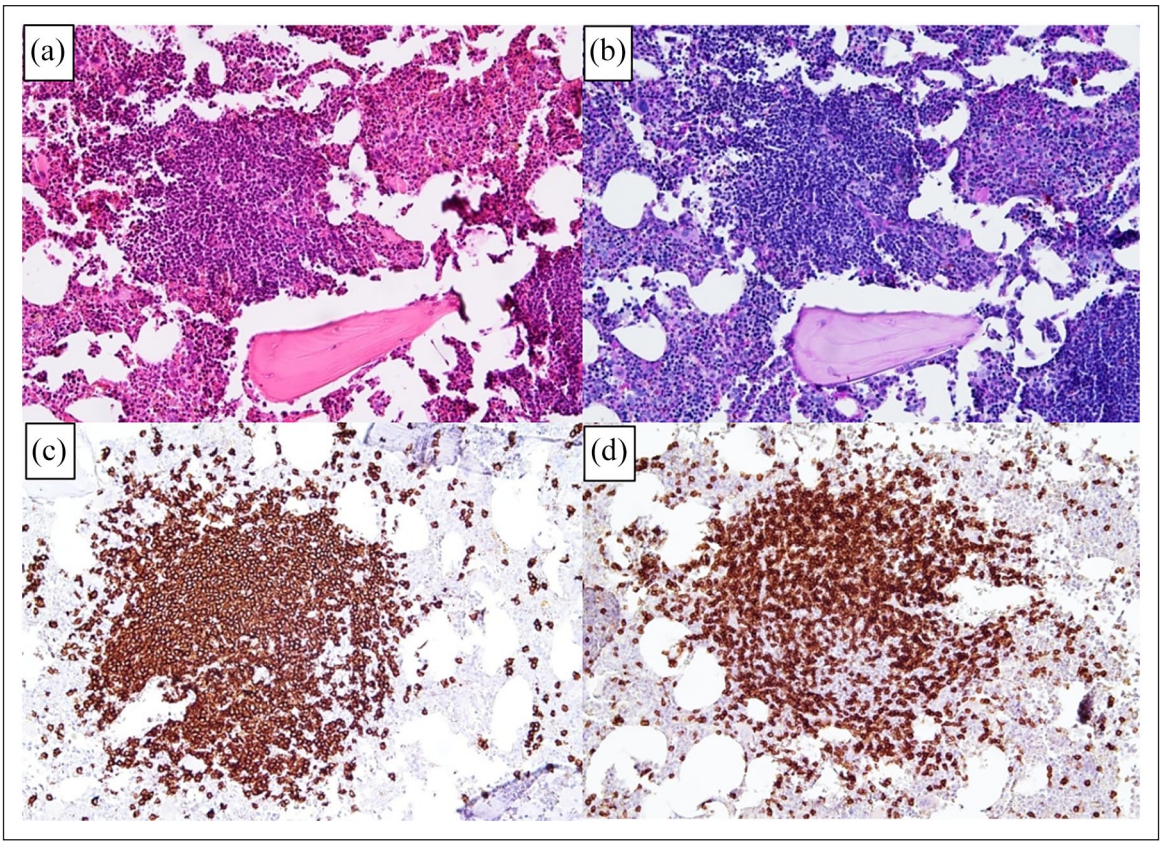

Figure 2. Bone marrow biopsy showing a large ill-defined nodule of infiltration by B cell lymphoma: (a) H&E ×20, (b) PAS ×20, (c) CD20 IHC ×20, (d) CD3 IHC ×20.

CT examination was then extended to the whole abdomen for the suspicion of splenomegaly that emerged from the previous HRCT scan. Splenomegaly was confirmed and two hypodense lesions in the VI segment of the liver were identified.

On transabdominal ultrasound with contrast medium, the two nodules were compatible with angioma. However, since the appearance of one of the two nodules was atypical and a possible metastatic replication was not completely excluded, a total body PET was performed, which did not show significant pathological findings.

The patient also underwent a dermatological consultation, to research for melanocytic nevi (due to previous immunoreactivity positivity in lungs): surgical removal of a left plantar pigmented lesion was performed, and the histological response was compound nevus. Subsequent ophthalmologic visits excluded choroidal melanoma.

Endocrinological consultation found an increased thyroid, with subverted ultrasound structure by the presence of multiple isoechogenic nodular areas haloed with microcollections of colloid with predominantly peripheral vascularization. A thyroid needle biopsy was performed and documented a hyperplastic and cystic follicular nodule.

After hematologic evaluation, in the hypothesis of a lymphoproliferative process (CT findings of lymphadenopathy in subcarinal and paratracheal sites, associated with splenomegaly), a bone marrow biopsy was performed (Figure 2). Subsequent histology showed bone marrow infiltrates of low-grade B-lymphocytic lymphoma, consistent with SMZL based on clinics, imaging, and immunophenotype (CD20 +/CD5-/Ciclin D1-/BCL6-/CD10-) for which no specific treatment was deemed necessary by the hematologist. However, given the rapidly evolving skin and lung scleroderma disease and according to the hematologist, we agreed on RTX administration (two injections at a dose of 1000 mg 15 days apart from one another, every 6 months).

Twenty-one months later, after the patient had undergone merely two courses of RTX (optimally tolerated), we documented a reduction of skin hardening (mRSS = 8.0). Together with the hematologist and pneumologist, we compared the most recent chest and abdomen CT scans with the ones previously acquired (Figure 3); we found a stable ILD and a slightly reduced splenomegaly, possibly due to RTX action against splenic B-cell proliferation. Lung function tests were not performed due to poor patient compliance to the examination. On completion, contrast-enhanced ultrasonography was performed to re-evaluate the hepatic nodules, which were unchanged from the previous controls and suggestive of angiomatous nature.

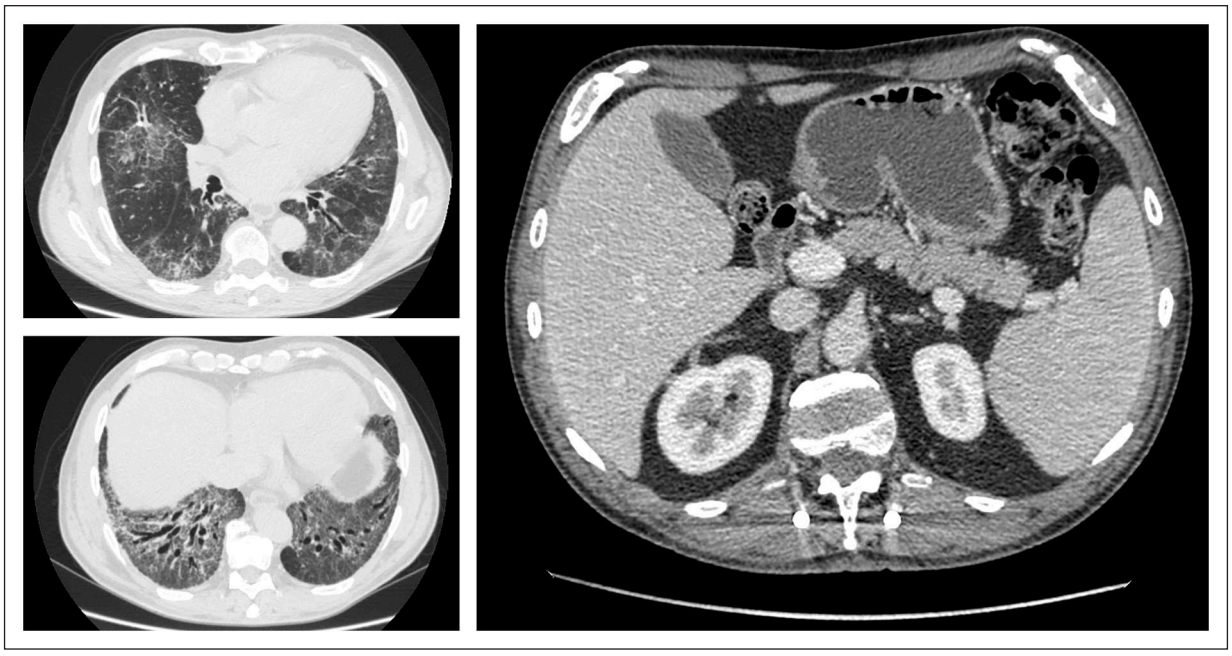

Figure 3. Left: HRCT images of stable ILD involvement, NSIP pattern. Right: abdomen CT showing slightly reduced splenomegaly.

Conclusion

Though hematological disorders occur rarely in SSc, unlike other autoimmune diseases,[7] nonetheless the incidence of hematological malignancies is significantly higher in SSs than in the general population; therefore, a careful evaluation is essential to guarantee an early detection.

Marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) is a B-cell neoplasm and type of indolent NHL. Extranodal marginal zone lymphoma may occur in many different sites,[8] but lung represents an uncommon site.[9]

In this case, the discovery of SMZL led us to reconsider the diagnosis of ILD and the previously resected lung nodule, in favor of an atypical, lung localization of a B-cell neoplasm in an SSc patient.

Indeed, our case poses several questions. First, a lung histopathological confirmation of extra-nodal localization in indolent lymphoma is not always technically feasible, due to lung anatomy and comorbidities.

However, even lacking lung histology, we performed CT/FDG-PET: the pulmonary nodulations did not appear metabolically evaluable, while only lower right paratracheal and subcarinal lymph nodes appeared to have moderate hyperfixation of the radiotracer.

Even though few studies[10] have reported how extranodal marginal zone B-cell lymphomas do not express noticeable FDG uptake on PET scans, we decided not to get a bioptic specimen from the lung, since the patient had already undergone lung nodule resection with benign histology; moreover, even a pulmonary localization would have not changed our therapeutic strategy.

An integrated, multidisciplinary examination of clinical and radiographic patterns made lung localization of extranodal marginal lymphoma a plausible hypothesis.

Therefore, we want to underline the importance of considering also lymphoproliferative disease as a possible differential diagnosis in the presence of atypical features of lung involvement in SSc, such as solitary parenchymal or mediastinal nodules and consolidative lesions along bronchovascular or subpleural bundles.

To the best of our knowledge, there are few cases of lung marginal B-cell lymphoma in rheumatological patients (in Table 1, we reported those described in the literature), but there is none describing marginal zone B-cell lymphoma (MZBL) with lung involvement in SSc patients.

The lung parenchyma hosts many lymphatics and lymphoid compartments.[13] Upon exposure to inhaled particles or intrinsic/extrinsic antigenic stimulation, a sequence of immunological processes arises. Working as a bricklayer, our patient has been frequently exposed to high levels of easy to inhale airborne dusts. Furthermore, the interplay between multiple factors such as chronic autoimmune stimulation, chronic inflammation, immunosuppressive drugs, and genetic factors may as well explain the development of hematological malignancies in CTDs.

The main CT patterns of lung lesions seen in MZBL are airspace consolidation or nodules containing air bronchograms within the lesions. A study by Bae et al.[11] classified the aspects of parenchymal lesions into four different patterns: single-nodular or consolidative aspects, multiple nodular or areas of consolidation, bronchiectasis and bronchiolitis, and diffuse interstitial lung disease (DILD) pattern. A study by Deng et al.[14] on pulmonary MALT

Table 1. Summary of described cases of lung marginal lymphoma in rheumatic patients.

Reference	N. pt	Age, y/sex	Disease	CT scan pattern	Respiratory symptoms	Treatment	Response
Bae et al.[11]	2	43/F	Sjogren	BEBR	No	Chemotherapy	Stable
		76/F	Sjogren	BEBR	Dyspnea	Surgical resection	No recurrence
	1	49/F	LES	DILD	Dyspnea, cough	Chemotherapy	Stable
Rubenstein et al.[8]	1	47/F	Sjogren	GG	No	Bortezomib	No recurrence
Laggner et al.[12]	1	57/F	LES	Consolidation	Dyspnea, chest pain	R-CVP, then RTX maintenance	No recurrence
*	1	63/M	SSc	GG	Dyspnea	RTX	Stable

BEBR: bronchiectasis and bronchiolitis; DILD: diffuse interstitial lung disease; GG: ground glass; LES: systemic lupus erythematous; R-CVP: rituximab-cyclophosphamide, vincristine, prednisone; RTX: rituximab; SSc: systemic sclerosis.
*Our case.

lymphoma proved that symptomatic patients had less consolidation and bronchiectasis, but more cystic bronchiectasis, rather than asymptomatic patients.

Therefore, an interesting item is whether HRCT may be valuable in the identification and differential diagnosis of primary pulmonary lymphoma, especially between MALT lymphoma and non-MALT lymphoma. Chen et al.[15] found that features like nodular or mass-like involvement pattern, DILD pattern, pneumonia-like consolidative pattern, and mixed pattern were not significantly different between MALToma and non-MALToma, while signs of air bronchogram and CT angiogram occurred significantly more often in individuals with MALToma than those with non-MALToma.

Accordingly, the differential diagnosis of MZBL includes many clinical presentations: organizing pneumonia, bronchioloalveolar carcinoma, benign spectrum of lymphoproliferative diseases (namely, nodular lymphoid hyperplasia and lymphoid interstitial pneumonia), sarcoidosis, and other granulomatous diseases, including granulomatous small vessel vasculitides. Moreover, manifestations such as interstitial lung abnormalities or bronchiectasis led to a particular diagnostic challenge in SSc patients with lung involvement, since this pulmonary radiological pattern is quite indistinguishable from the hematological presentation: immunohistochemical staining on core biopsy specimens may be needed to confirm the diagnosis.

Imaging diagnostic challenge is highlighted by Rubenstein et al.[8] who described a case of extranodal marginal zone lymphoma of the lung in a Sjogren patient. Similar to our presented report, they demonstrate the difficulty in distinguishing lymphocytic interstitial pneumonitis (LIP) from extranodal marginal zone lymphoma, due to the frequent overlap between these two entities' appearance on CT scan imaging.

There are, however, a number of pathological features that favor LIP over marginal zone lymphoma. Immunohistochemical analysis is of particular importance to demonstrate the primarily follicular distribution of B-cells and the polyclonality of the lymphocytic proliferation in LIP. Other pathological features supporting MALT lymphoma may include distortion of lung architecture, frequent lymphoepithelial lesions, and the presence of pleural infiltration. Intranuclear B-lymphocyte inclusions, known as Dutcher bodies, are not usually found in benign processes and suggest MALT lymphoma over LIP.[13]

However, an important aspect to consider is the usual indolent nature of the lesions.[11] RTX is active against CD20-expressing cells and therefore potentially active also against lymphomatous cells.[16] In the literature, we found some cases of patients affected by SMZL successfully treated with RTX.[17] As in SSc, apart from first-line strategies for SSc-related ILD including mofetil-mycophenolate or cyclophosphamide, growing evidence has been accumulated about the comparable efficacy of RTX.[18]

In conclusion, with this case report and review of the literature, we would like to highlight the rarity of the pulmonary location of marginal B-cell lymphoma in rheumatic patients, underlining the need of a careful multidisciplinary evaluation to detect indolent lymphoproliferative forms.

We decided not to perform lung biopsy, therefore renouncing to a histopathologic confirmation of our suspicion of lung SMZL, due to invasiveness of the procedure and the relative safety of an *ex-juvantibus* strategy, since we expected RTX to be effective against both a lung localization of a lymphoproliferative disordered (deemed to be indolent) or SSc-related interstitial lung involvement.

Indeed, nonspecific presentation and indolent course make the diagnosis of primary pulmonary lymphoma very challenging (thus often leading to misdiagnosis or delayed diagnosis), especially in the context of SSc-related ILD, since CT imaging findings of both diseases may overlap. Further studies will be needed to fully elucidate the pathogenesis of this association and to provide better diagnostic approaches.

Author contributions

G.G. wrote the manuscript, with the support of B.M., G.C., and M.P.; G.L.C. dealt with pneumological facets of the case; F.C.

analyzed and interpreted the patient data regarding the hematological disease; G.L. and R.G. performed the histological examination; and M.G. supervised the manuscript. All authors read and approved the final manuscript. All authors discussed the results and contributed to the final manuscript.

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Informed consent

The patient in this manuscript has given written informed consent to the publication of the case details.

ORCID iD

Giorgio Galoppini https://orcid.org/0000-0003-1638-7310

References

1. Denton CP and Khanna D. Systemic sclerosis. *Lancet* 2017; 390(10103): 1685–1699.
2. Olesen AB, Svaerke C, Farkas DK, et al. Systemic sclerosis and the risk of cancer: a nationwide population-based cohort study. *Br J Dermatol* 2010; 163(4): 800–806.
3. Maria ATJ, Partouche L, Goulabchand R, et al. Intriguing relationships between cancer and systemic sclerosis: role of the immune system and other contributors. *Front Immunol* 2018; 9: 3112.
4. Noureldine HA, Nour-Eldine W, Hodroj MH, et al. Hematological malignancies in connective tissue diseases. *Lupus* 2020; 29(3): 225–235.
5. Colaci M, Giuggioli D, Vacchi C, et al. Haematological malignancies in systemic sclerosis patients: case reports and review of the world literature. *Case Rep Rheumatol* 2017; 2017: 6230138.
6. Matutes E, Oscier D, Montalban C, et al. Splenic marginal zone lymphoma proposals for a revision of diagnostic, staging and therapeutic criteria. *Leukemia* 2008; 22(3): 487–495.
7. Wawrzycki B, Krasowska D, Pietrzak A, et al. Urticarial rash, fever, and arthritis: a case of refractory Adult-onset Still's disease with good response to tocilizumab. *Dermatol Ther* 2019; 32(5): e13041.
8. Rubenstein JN, Beatty C, Kinkade Z, et al. Extranodal marginal zone lymphoma of the lung: evolution from an underlying reactive lymphoproliferative disorder. *J Clin Exp Pathol* 2015; 5(1): 208.
9. Sanguedolce F, Zanelli M, Zizzo M, et al. Primary pulmonary B-cell lymphoma: a review and update. *Cancers* 2021; 13(3): 415.
10. Hoffmann M, Kletter K, Becherer A, et al. 18F-fluorodeoxyglucose positron emission tomography (18F-FDG-PET) for staging and follow-up of marginal zone B-cell lymphoma. *Oncology* 2003; 64(4): 336–340.
11. Bae YA, Lee KS, Han J, et al. Marginal zone B-cell lymphoma of bronchus-associated lymphoid tissue: imaging findings in 21 patients. *Chest* 2008; 133(2): 433–440.
12. Laggner U, Khiroya R, Wotherspoon AC, et al. MALT lymphoma arising on a background of reactive pulmonary lymphoid hyperplasia in a patient with systemic lupus erythematosus. *Histopathology* 2018; 72(4): 704–706.
13. Hare SS, Souza CA, Bain G, et al. The radiological spectrum of pulmonary lymphoproliferative disease. *Br J Radiol* 2012; 85(1015): 848–864.
14. Deng W, Wan Y and Yu JQ. Pulmonary MALT lymphoma has variable features on CT. *Sci Rep* 2019; 9(1): 8657.
15. Chen Y, Chen A, Jiang H, et al. HRCT in primary pulmonary lymphoma: can CT imaging phenotypes differentiate histological subtypes between mucosa-associated lymphoid tissue (MALT) lymphoma and non-MALT lymphoma. *J Thorac Dis* 2018; 10(11): 6040–6049.
16. Keating GM. Rituximab: a review of its use in chronic lymphocytic leukaemia, low-grade or follicular lymphoma and diffuse large B-cell lymphoma. *Drugs* 2010; 70(11): 1445–1476.
17. Okamura I, Imai H, Mori K, et al. Rituximab monotherapy as a first-line treatment for pulmonary mucosa-associated lymphoid tissue lymphoma. *Int J Hematol* 2015; 101(1): 46–51.
18. Goswami RP, Ray A, Chatterjee M, et al. Rituximab in the treatment of systemic sclerosis–related interstitial lung disease: a systematic review and meta-analysis. *Rheumatology* 2020; 60(2): 557–567.