Case Reports in Oncology

Case Rep Oncol 2023;16:116–123
DOI: 10.1159/000529425
Received: August 27, 2022
Accepted: January 23, 2023
Published online: February 28, 2023

Case Report

Two Very Rare Cases of Metastatic Thymic Carcinoma with Sjogren's Syndrome: A Case Series

Amy E. Smith[a, b] Alisa Kane[c, d] Francesca Watts[e] Min Qiu[b, e, f] Venessa Chin[a, d, g]

[a]The Kinghorn Cancer Centre, St Vincent's Hospital, Sydney, NSW, Australia; [b]School of Medicine, University of Notre Dame Australia, Sydney, NSW, Australia; [c]Department of Immunology and HIV, St Vincent's Hospital, Sydney, NSW, Australia; [d]School of Medicine and Health, The University of New South Wales, Sydney, NSW, Australia; [e]Department of Anatomical Pathology, St Vincent's Hospital, Sydney, NSW, Australia; [f]SydPath, St Vincent's Hospital, Sydney, NSW, Australia; [g]The Garvan Institue of Medical Research, Sydney, NSW, Australia

Keywords

Thymic carcinoma · Paraneoplastic syndrome · Sjogren's syndrome · Immunotherapy · Autoimmune disorder

Abstract

Thymic tumours are rare thoracic malignancies with thymic carcinoma accounting for approximately 12% of all thymic tumours compared to thymomas which account for approximately 86%. Unlike thymomas, it is very rare for thymic carcinomas to be associated with autoimmune disorders or paraneoplastic syndromes. When these phenomena do occur, the vast majority are myasthenia gravis, pure red cell aplasia, or systemic lupus erythematous. Paraneoplastic Sjogren's syndrome is a rare complication of thymic carcinoma, with only two cases previously reported. Here we present 2 cases of patients with metastatic thymic carcinoma who developed autoimmune phenomena consistent with Sjogren's syndrome without classical symptoms prior to treatment. One patient opted for surveillance of their malignancy, while the other underwent chemoimmunotherapy with favourable results. These case reports describe two distinctive clinical presentations of a rare paraneoplastic phenomenon.

Correspondence to:
Amy E. Smith, amy.smith@health.nsw.gov.au

Case Rep Oncol 2023;16:116–123
DOI: 10.1159/000529425

Introduction

Thymic tumours are a collection of rare thoracic malignancies, constituting only 0.2–1.5% of all solid tumours [1]. They can be aggressive and difficult to treat [2]. Thymic tumours are the most common tumours in the anterior mediastinal compartment and include thymoma, thymic carcinomas, and neuroendocrine thymic tumours [2]. Thymomas account for around 86% of thymic tumours, whereas thymic carcinomas account for around 12%, and neuroendocrine thymic tumours account for around 2% [3]. Thymic carcinomas are distinguished from thymomas using the 4th edition of the World Health Organization (WHO) classification system [4]. These criteria are based on the morphology of epithelial tumour cells, amount of lymphocytic involvement, and resemblance to normal thymic tissue [1]. Additionally, thymic carcinomas have distinctive immunological, genetic, and molecular characteristics when compared to thymomas, and they often present differently clinically [1]. Important molecular characteristics that help to distinguish thymic carcinoma from thymoma include CD5 and cKIT positivity. The most common subtype of thymic carcinoma is squamous cell carcinoma which is suggested by positivity for p40 on molecular testing.

Thymomas are commonly associated with autoimmune conditions. Approximately 30–40% of patients present with autoimmune disorders, with half of these being myasthenia gravis [1]. Other common autoimmune presentations include pure red cell aplasia and hypogammaglobulinaemia [2]. In contrast, patients with thymic carcinomas rarely develop autoimmune or paraneoplastic phenomena [1, 2]. Here we present 2 cases of patients with metastatic thymic carcinoma who developed autoimmune phenomena consistent with Sjogren's syndrome.

Case 1

A 72-year-old Caucasian male ex-smoker with no relevant past medical history presented to his general practitioner with right lower lateral chest pain. Chest X-ray and computer-tomography (CT) scan of the chest showed a 48 × 31 × 47 mm anterior mediastinal mass with right-sided pleural disease. He subsequently underwent a fluorodeoxyglucose (FDG)-positron emission tomography scan which showed this mass was FDG-avid (Fig. 1a). The patient was lost to follow up. Three months later, a repeat CT scan of the chest, abdomen, and pelvis demonstrated extensive pleural disease, a lobulated soft tissue mass within the anterior mediastinum, as well as bony metastatic disease. A biopsy of a paravertebral soft tissue mass confirmed metastatic thymic cancer with squamous differentiation (Fig. 2). Chemotherapy was offered; however, the patient declined, instead opting for close surveillance.

Three months after his diagnosis, he presented with acute abdominal pain and underwent emergency laparotomy and small bowel repair following a small bowel perforation with pelvic collection secondary to diverticulitis. Biopsy of the colon showed florid serositis and microscopic and macroscopic changes consistent with peritonitis without signs of malignant cells. Approximately 1 week later, there was an incidental finding of a new pericardial effusion (Fig. 1b). A pericardial window was performed. Histology of the pericardial biopsy showed fibrin, granulation tissue, neutrophils, histocytes, and occasional multinucleated giant cells with no evidence of malignancy, consistent with acute pericarditis (Fig. 2d). Soon after, a CT showed a new left-sided pleural effusion which was drained under ultrasound guidance (Fig. 1c). Cytology of the pericardial and pleural fluid showed inflammatory cells only.

These results prompted autoimmune work-up and immunology referral. His initial results returned positive autoimmune serology with an antinuclear antibody titre greater than

Case Rep Oncol 2023;16:116–123
DOI: 10.1159/000529425

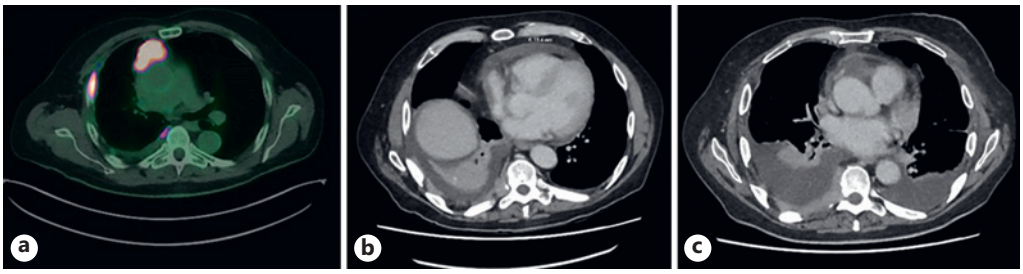

Fig. 1. Imaging series of thymic carcinoma, pericardial effusion, and pleural effusions. **a** Axial PET CT showing anterior mediastinal mass and right pleural disease. **b** Axial CT upper abdomen showing 15.4 mm pericardial effusion. **c** Axial CT upper abdomen showing bilateral pleural effusions.

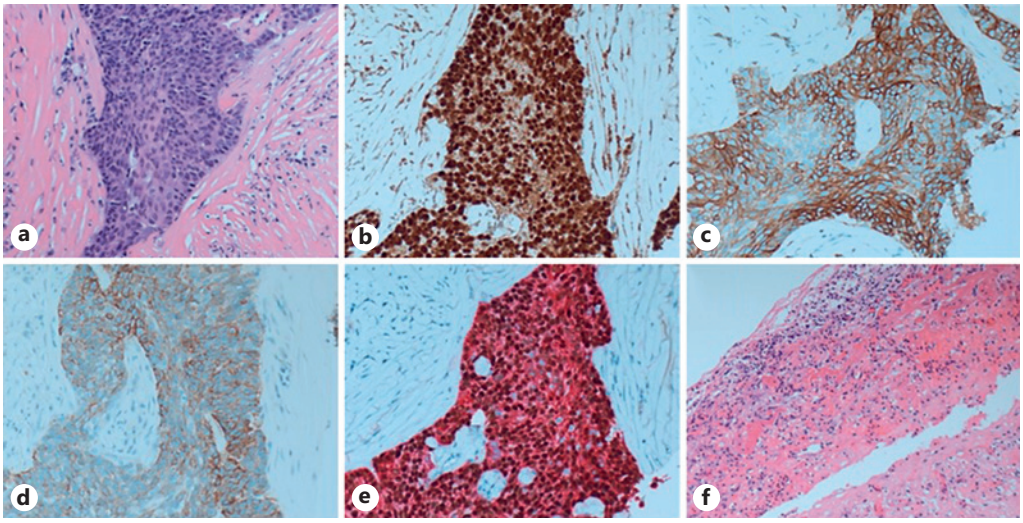

Fig. 2. Morphological and immunohistochemical features of thymic carcinoma and pericarditis. **a** Haematoxylin and eosin stain – high-grade carcinoma with solid sheets. **b** Immunohistochemical staining for PAX8. **c** Immunohistochemical staining for CD5. **d** Immunohistochemical staining for CD117. **e** Dual immunohistochemical staining for p40 (brown chromogen) and CK5/6 (red chromogen). **f** Haematoxylin and eosin stain of the pericardial biopsy – acute inflammation with fibrinoid material and granulation tissue. Figure panels **a**–**e** magnification, ×20, panel **f** magnification, ×10.

1:640 with speckled pattern, extractable nuclear antibodies strongly positive for SSA (Ro-60), strongly positive for SSA (Ro-52), and weakly positive for SSB, as well as a positive rheumatoid factor of 16.5 IU/mL, polyclonal hypergammaglobulinaemia, erythrocyte sediment rate of 106 mm/h, and C-reactive protein of 100 mg/L. Double-stranded DNA was negative with a result of <10 IU/mL.

A Schirmer's test was performed which showed 1 mm of tear production over 5 min, consistent with severe dry eyes. Based on his clinical, serological, and biopsy findings, a diagnosis of paraneoplastic Sjogren's syndrome was made by fulfilment of the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) Classification Criteria for Primary Sjogren's Syndrome [3]. Chemoimmunotherapy was offered, and the patient again declined, instead opting for close surveillance. Three months post discharge from hospital, CT showed that, overall, there had not been a significant change in the disease

Case Rep Oncol 2023;16:116–123
DOI: 10.1159/000529425

burden, except for possible slightly increased disease at the right base of the lung. He remains on close surveillance monitoring. The completed CARE Checklist for this case report is included as online supplementary material (for all online suppl. material, see www.karger.com/doi/10.1159/000529425).

Case 2

A 48-year-old female with a past medical history of juvenile anaemia, juvenile asthma, recurrent sinopulmonary infections, dry eyes, occasional mouth ulcers, recurrent vaginal thrush, migraines, methylenetetrahydrofolate reductase (MTHFR) mutation, and haemochromotosis carrier status presented to her general practitioner with a history of fatigue. After an initial diagnosis of chronic fatigue syndrome, she developed palpable left supraclavicular lymphadenopathy. She underwent a CT chest which showed a mediastinal mass and lung metastases. FDG-positron emission tomography scan confirmed metastatic malignancy involving the liver, lungs, bones, lymph nodes, and anterior mediastinum (Fig. 3a). A biopsy of the supraclavicular mass showed a metastatic high-grade carcinoma positive for CD5 and CKIT, in keeping with thymic carcinoma (Fig. 4) [5].

Prior to the commencement of palliative-intent chemoimmunotherapy, the patient was referred to an immunologist to investigate for a possible underlying immunodeficiency given self-reported history of recurrent sinopulmonary infections and recurrent vaginal candidiasis. Her blood results showed antinuclear antibody with titre greater than 1:640 speckled pattern with extractable nuclear antibodies positive for SSA (Ro-60), strongly positive for SSA (Ro-52), and weakly positive for SSB, as well as a positive rheumatoid factor of 48 IU/mL, erythrocyte sediment rate of 50 mm/h, normal C-reactive protein of 2 mg/L, and very elevated double-stranded DNA of 415 IU/mL. This serology was consistent with Sjogren's syndrome and systemic lupus erythematous (SLE) [6, 7].

The patient subsequently underwent palliative-intent chemoimmunotherapy with 3-weekly carboplatin, paclitaxel, and atezolizumab with a good clinical and radiological response. In addition, she was prescribed fluconazole and sulfamethoxazole/trimethoprim for fungal and pneumocystis jejuni prophylaxis, respectively, due to intermittent high-dose steroid use. Following cycle one, she experienced widespread maculopapular rash that was thought to be an immunotherapy-related adverse event. This responded well to prednisone which was weaned over several weeks, and she was able to recommence her atezolizumab. Later in her treatment, she developed a second distinctive rash that appeared following sun exposure. The patient was reviewed by dermatology, and the rash was felt to be a photosensitive rash, possibly in keeping with SLE given her previous positive serology, and she was subsequently commenced on hydroxychloroquine. The completed CARE Checklist for this case report is included as online supplementary material.

Discussion

The thymus is a primary lymphoid tissue that plays an integral role in immune system development. It is located in the upper anterior mediastinum and extends anteriorly towards the thyroid gland. The thymus is critical for the development of mature T cells. Architecturally, it has an outer cortex and an inner medulla which support different stages of T-cell development [8]. In the cortex, positive selection occurs so that only the thymocytes with a functioning T-cell receptor survive. Following this, negative selection occurs in the medulla which leads to elimination of T cells which have developed tissue-specific self-antigens. The

Case Rep Oncol 2023;16:116–123
DOI: 10.1159/000529425

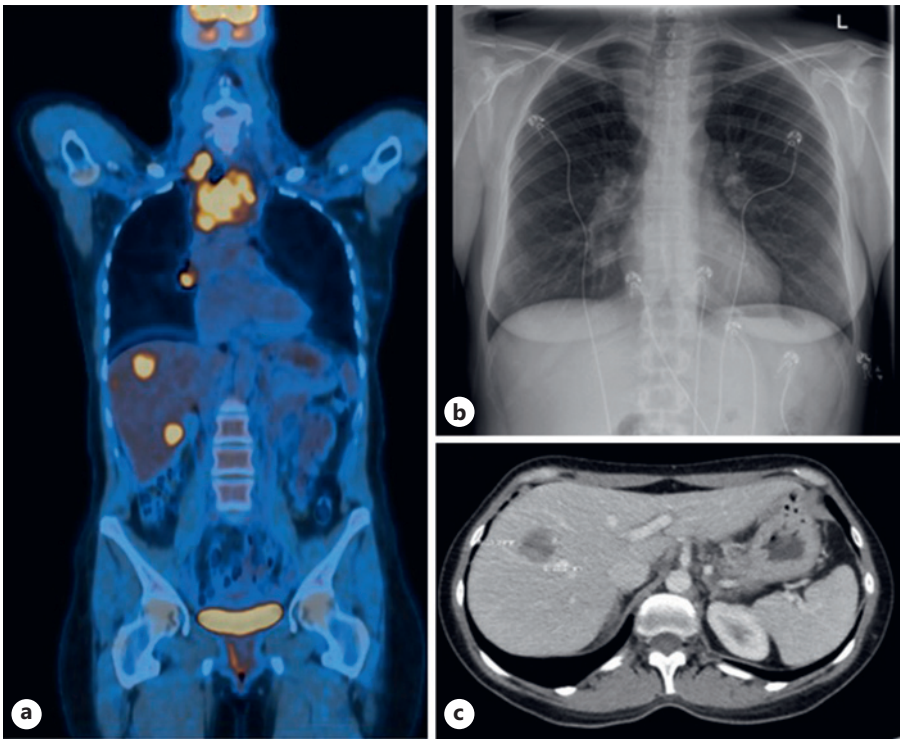

Fig. 3. Image series of metastatic thymic carcinoma. **a** Coronal PET CT showing thymic carcinoma with liver lesions. **b** Chest X-ray showing thymic mass. **c** Axial CT upper abdomen showing liver metastases.

thymus' ability to recognize and eliminate T lymphocytes that can attack self-antigens is crucial in the prevention of autoimmunity [4, 9].

Not only do thymomas and thymic cancers differ clinically, they also have different immunological, morphological, genetic, and molecular characteristics [1]. Both thymomas and thymic carcinomas are classified morphologically using the WHO classification of thymic tumour (types A, AB, B1, B2, B3, C). Thymomas are localised to the thymic gland and surrounding organs and are characterised by their lobulated architecture, whereas thymic carcinomas are far more aggressive and are more likely to metastasize to the liver, lymph nodes, and bones [1]. Immunologically, it has been identified that defective major histocompatibility complex (MHC) class II or autoimmune regulator (AIRE) gene expression leads to increased autoimmunity in thymoma. It is not clear the role AIRE gene expression has in thymic carcinomas and autoimmunity [1].

Autoimmune disease occurs in approximately 30–40% of patients with a thymoma, with approximately 50% of these cases developing myasthenia gravis, only up to 2% developing SLE, and less than 1% developing Sjogren's syndrome [9]. By contrast, approximately 5–6% of patients with thymic carcinoma will develop an autoimmune/paraneoplastic phenomenon, with the incidence of SLE unknown and only two previous cases of thymic carcinoma-associated Sjogren's syndrome reported [10]. In a case-review of thymoma-associated SLE, most of the cases were reported in women with the most common presentations including articular involvement, skin manifestation, and serositis [9]. Our patient in case 2 did not demonstrate classical symptoms of SLE at the time of her diagnosis, but rather described oral ulcerations and had serology consistent with SLE. It was not until she underwent treatment with immune checkpoint inhibitors (ICI) that autoimmune phenomenon became apparent. To our knowledge, she is the first case of thymic carcinoma associated with 2 rare paraneoplastic/autoimmune phenomena: Sjogren's syndrome and SLE.

Case Rep Oncol 2023;16:116–123
DOI: 10.1159/000529425

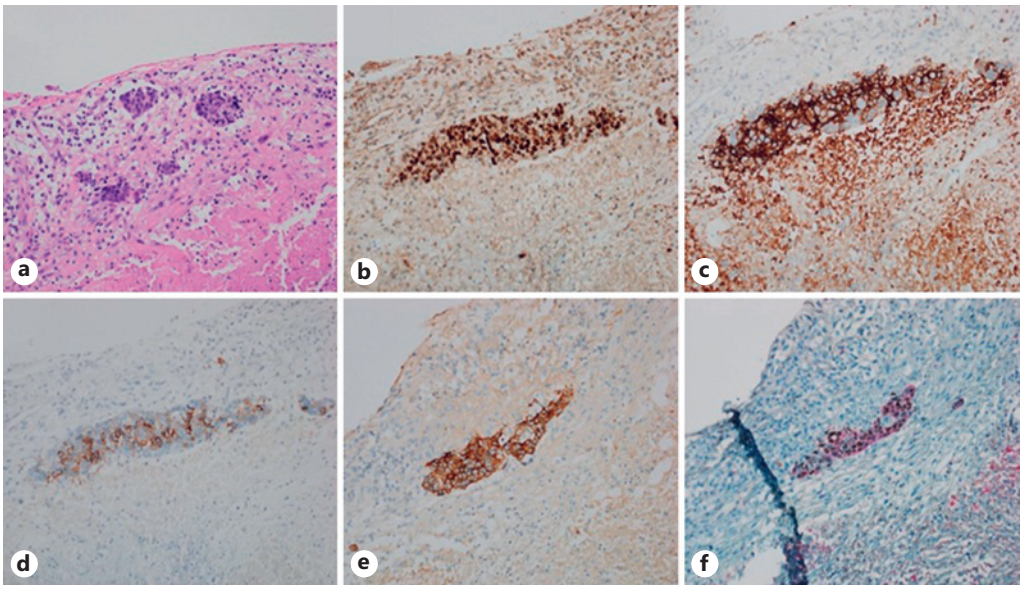

Fig. 4. Morphological and immunohistochemical features of thymic carcinoma. **a** Tumour nests with abundant necrosis, with similar morphology to the tumour in case 1 (Fig. 2). **b** Immunohistochemical staining for PAX8. **c** Immunohistochemical staining for CD5. **d** Immunohistochemical staining for CD117. **e** Immunohistochemistry for cytokeratin. **f** Dual immunohistochemical staining for p40 (brown chromogen) and CK5/6 (red chromogen). **a–f** magnification, ×20.

In cases of thymoma-induced autoimmune disease, the mainstay of treatment is surgical resection [2]. Surgical resection of early thymic carcinoma has been reported to offer control of autoimmune phenomena [11]. However, this relapsed with postoperative metastases of the tumour [12], whereas in metastatic thymic carcinoma, surgery is not an option. In this rare group of patients, there is the dilemma of not only systemically treating the underlying malignancy but also managing the autoimmune/paraneoplastic phenomena.

First-line systemic treatment for thymic tumours is platinum-based chemotherapy [12] but more recently, ICIs have been studied due to their efficacy in other solid organ malignancies [13]. In 2020, Sato et al. [14] published a multicentre phase 2 trial which confirmed efficacy of lenvatinib as second-line treatment for patients with advanced and metastatic thymic carcinomas. Unfortunately, ICIs are not recommended in thymoma due to high rates of severe autoimmune disorders following initiation of this treatment [15]. The same has not been observed with management of thymic carcinoma with ICIs [16]. Immunohistochemistry studies have previously shown programmed-death ligand 1 (PD-L1) positivity in 70% of thymic carcinomas, suggesting possible efficacy of this treatment modality [12, 17]. In a study that used single-agent pembrolizumab, it was shown that this treatment in thymic carcinoma patients with high PD-L1 expression evoked a durable disease response across the study period, making it a good treatment option [18]. Preliminary results from other similar studies have thus far confirmed these findings [17, 18]. Unfortunately, there were no data recorded on whether the patients in these studies displayed autoimmune phenomena prior to commencing ICIs or what the outcome of the autoimmune/paraneoplastic phenomena was post-ICIs.

There is not yet a consensus on how to manage thymic carcinoma with associated autoimmune/paraneoplastic phenomena. One thought is that successful treatment of the thymic carcinoma with chemotherapy or chemoimmunotherapy will improve the autoimmune symptoms. This was the approach offered to the patient described in case 1 which he

declined. He was not offered immunosuppression or disease-modifying anti-rheumatic drugs to treat his autoimmune/paraneoplastic Sjogren's syndrome due to his untreated active malignancy. Our patient in case 2 was managed with standard chemoimmunotherapy and accepted advice to commence a disease-modifying anti-rheumatic drug to treat her autoimmune/paraneoplastic phenomenon to good effect.

Conclusion

These cases emphasize the importance of having clinical suspicion and recognizing autoimmune and paraneoplastic phenomena not only in thymoma but also in thymic carcinoma. It also highlights the need for greater understanding of not only the underlying mechanism of these associations but also possible avenues for treatment. It also shows the importance of case reports in seemingly rare conditions to enhance the literature base for clinicians trying to treat similar patients in the future. These cases also showcase the importance of multidisciplinary speciality teams in identifying, investigating, and managing this cohort of patients to decrease morbidity and improve overall survival.

Acknowledgments

The authors would like to acknowledge the generous contribution that the 2 patients have made in allowing us to document their case.

Statement of Ethics

Formal ethics approval was not required in accordance with national guidelines. Written informed consent was obtained from both patients for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors declare that they have no competing interests.

Funding Sources

No funding was provided to the authors completing this report.

Author Contributions

Amy Smith collected the patient data and was a major contributor in writing the manuscript. Alisa Kane analysed and interpreted the data regarding immunological disease contributed to the interpretation of treatment for patients. Venessa Chin analysed and interpreted the data regarding oncological disease and contributed to the interpretation of treatment for patients. Min Qiu provided images of patient biopsy specimen and description of morphology and immunohistochemistry of patient pathology. Francesca Watts provided

images of patient biopsy specimen and description of morphology and immunohistochemistry of patient pathology. All authors read and approved the final manuscript.

Data Availability Statement

All data generated or analysed during this report are included in the article. Further enquiries can be directed to the corresponding author.

References

1 Kelly RJ. Thymoma versus thymic carcinoma: differences in biology impacting treatment. J Natl Compr Canc Netw. 2013;11(5):577–83.
2 Basse C, Girard N. Thymic tumours and their special features. Eur Respir Rev. 2021;30(162):200394.
3 Padda SK, Yao X, Antonicelli A, Riess JW, Shang Y, Shrager JB, et al. Paraneoplastic syndromes and thymic malignancies: an examination of the international thymic malignancy interest group retrospective database. J Thorac Oncol. 2018;13(3):436–46.
4 Blum TG, Misch D, Kollmeier J, Thiel S, Bauer TT. Autoimmune disorders and paraneoplastic syndromes in thymoma. J Thorac Dis. 2020;12(12):7571–90.
5 Kuo TT, Chan JK. Thymic carcinoma arising in thymoma is associated with alterations in immunohistochemical profile. Am J Surg Pathol. 1998;22(12):1474–81.
6 Aringer M, Costenbader KH, Daikh DI, Brinks R, Mosca M, Ramsey-Goldman R, et al. 2019 European league against rheumatism/American college of rheumatology classification criteria for systemic lupus erythematosus. Arthritis Rheumatol. 2019;71(9):1400–12.
7 Shiboski CH, Shiboski SC, Seror R, Criswell LA, Labetoulle M, Lietman TM, et al. 2016 American college of rheumatology/European league against rheumatism classification criteria for primary Sjögren's syndrome: a consensus and data-driven methodology involving three international patient cohorts. Ann Rheum Dis. 2017;76(1):9–16.
8 Valavanis C, Stanc GM, Baltayiannis N. Classification, histopathology and molecular pathology of thymic epithelial tumors: a review. J Balkan Union Oncol. 2021;26(4):1198–207.
9 Mollaeian A, Haas C. A tale of autoimmunity: thymoma, thymectomy, and systemic lupus erythematosus. Clin Rheumatol. 2020;39(7):2227–34.
10 Chang CC, Chang YL, Lee YC. Thymic carcinoma associated with Sjogren's syndrome and syndrome of inappropriate antidiuretic hormone. J Thorac Cardiovasc Surg. 2010;139(2):e1–2.
11 Xin Y, Cai H, Li Y, Cui Y. Thymic hyperplasia associated with primary Sjogrens syndrome cured by thymectomy. J Thorac Dis. 2017;9(2):E130–2.
12 Isono T, Wakasa T, Kusumoto H, Shimada K, Ogawa T, Shiono H. SS-A52 antigen expression in thymic carcinoma accompanied with Sjogren syndrome: a case report. Medicine. 2021;100(5):e24491.
13 Benitez JC, Besse B. Narrative review of immunotherapy in thymic malignancies. Transl Lung Cancer Res. 2021;10(6):3001–13.
14 Sato J, Satouchi M, Itoh S, Okuma Y, Niho S, Mizugaki H, et al. Lenvatinib in patients with advanced or metastatic thymic carcinoma (REMORA): a multicentre, phase 2 trial. Lancet Oncol. 2020;21(6):843–50.
15 Cho J, Kim HS, Ku BM, Choi YL, Cristescu R, Han J, et al. Pembrolizumab for patients with refractory or relapsed thymic epithelial tumor: an open-label phase II trial. J Clin Oncol. 2019;37(24):2162–70.
16 Katsuya Y, Horinouchi H, Seto T, Umemura S, Hosomi Y, Satouchi M, et al. Single-arm, multicentre, phase II trial of nivolumab for unresectable or recurrent thymic carcinoma: PRIMER study. Eur J Cancer. 2019;113:78–86.
17 Lippner EA, Lewis DB, Robinson WH, Katsumoto TR. Paraneoplastic and therapy-related immune complications in thymic malignancies. Curr Treat Options Oncol. 2019;20(7):62.
18 Giaccone G, Kim C. Durable response in patients with thymic carcinoma treated with pembrolizumab after prolonged follow-up. J Thorac Oncol. 2021;16(3):483–5.