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Case Report

Paraneoplastic Systemic Sclerosis in a Patient with Metastatic Thymic Carcinoma

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Abstract

Thymic malignancies cause alterations in the immune system. Thymomas are known to be associated with paraneoplastic syndrome and autoimmunity, including myasthenia gravis, systemic lupus erythematosus, inappropriate antidiuretic hormone secretion, pure red cell aplasia, pernicious anemia, pemphigus, and autoimmune thyroid diseases. However, paraneoplastic syndrome has rarely been observed in patients with thymic carcinoma. The management of patients with paraneoplastic autoimmune disease is difficult, and treatment of the underlying malignancy is important. Herein, we present a case of thymic carcinoma who developed systemic sclerosis 3 years after the initial diagnosis during disease progression.

Keywords: Autoimmune, paraneoplastic syndrome, systemic sclerosis, thymic carcinoma

Introduction

Thymoma and thymic carcinomas are thymic epithelial tumors originating in the thymus. Thymomas are relatively rare (1.5 cases/million), and thymic carcinoma, which is classified as a type C thymoma in the WHO classification system, is even rarer. Thymomas often present with locally advanced disease, and it is much less aggressive than thymic carcinoma. Thymic carcinoma is distinct from other thymomas, since thymic carcinoma has more overtly malignant cytologic characteristics (anaplasia, cellular atypia, and mitotic activity) and poor prognosis.[1]

Thymomas are associated with a variety of paraneoplastic syndromes and in particular myasthenia gravis which is found in 30% of thymoma patients.[2-5] However, the incidence of paraneoplastic autoimmune syndrome is much lower among patients with thymic carcinoma.[6] In one study based on the retrospective database of the International Thymic Malignancy Interest Group, the incidence of paraneoplastic autoimmune syndrome was 5.8% in patients with thymic carcinoma, compared to 38% in patients with thymoma.[2] In another study that included 614 patients with anterior mediastinal tumors in Taiwan, 7.8% of the patients with thymic carcinoma were

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associated with myasthenia gravis.[7,8] Other paraneoplastic autoimmune syndromes have rarely been described. Herein, we report a case of metastatic thymic carcinoma who developed a rare paraneoplastic autoimmune syndrome and review the associated literature.

Case Report

A 61-year-old man, who was healthy except for a history of hypertension, presented with dull chest pain and breathing difficulty in November 2014. Chest plain film and computed tomography (CT) revealed a mediastinal tumor measuring 8.4 cm × 6.3 cm × 6.1 cm abutting the ascending aorta and superior vena cava, with involvement of the right upper lobe of the lung. After serial workup, the final diagnosis was thymic carcinoma, with neuroendocrine differentiation, Masaoka Stage III, cT3N0M0.

The initial treatment plan was neoadjuvant chemotherapy followed by surgical resection. He received two courses of neoadjuvant chemotherapy with cisplatin and etoposide; however, the size of the tumor did not change. He then received radiation therapy (50 Grays in 25 fractions over 35 days) to the tumor, and the tumor size decreased. He subsequently received thymectomy with right diaphragm plication through sternotomy in July 2015. The pathology report showed thymic carcinoma with pericardium invasion and positive margins. After surgery, he received adjuvant radiation therapy to the tumor bed and positive margin (36 Grays in 18 fractions over 26 days).

Liver metastasis was detected 3 months after the operation. In addition, pleural and pericardial effusions were also found while the cytology was negative. He received CT-guided radiofrequency ablation with a concomitant biopsy, and the pathology report confirmed liver metastasis of thymic carcinoma. The patient also complained of lower back numbness, and L-S spine magnetic resonance imaging revealed intradural tumors at L5 and L3–L4 levels. He subsequently received laminectomy for L3–L4 tumor resection, followed by radiation therapy to the lumbar spine tumor bed.

To control systemic progression, he was given palliative chemotherapy with cisplatin and weekly 24-h infusions of high-dose 5-fluorouracil and leucovorin. After four courses of cisplatin-based chemotherapy, CT revealed stable disease. He was thus given oral tegafur-uracil as maintenance therapy, and a follow-up CT scan revealed stable disease.

However, he complained of having a puffy face in March 2017 and generalized edema in September 2017. We gave him diuretics and albumin supplements, but the symptoms did not improve. Stiffness of his fingers and face developed in November 2017 [Figures 1 and 2], and we checked his autoimmune profile for possible autoimmune disorders. The laboratory results disclosed a high antinuclear antibody level [Table 1], and he was referred to a rheumatologist in December 2017. Although further laboratory tests including anti-Scl-70 and anti-CENP were negative, a diagnosis of cancer-associated scleroderma was made according to the clinical picture. Hydroxychloroquine, prednisolone, and colchicine were prescribed, and his condition remained stable.

Since malignancy was considered to be the underlying cause of autoimmunity, we resumed chemotherapy with doxorubicin (50 mg/m^2), cyclophosphamide (500 mg/m^2), and carboplatin (area under the curve = 3). His finger stiffness improved after chemotherapy, and we plan to give him four cycles of chemotherapy followed by oral maintenance therapy.

Materials and Methods

A literature search was conducted in PubMed using the search terms: (((autoimmune[Title/Abstract]) OR paraneoplastic[Title/Abstract])) AND thymic carcinoma[Title/Abstract].

Seventy-three articles were found. We reviewed the title and abstract of every article and also reviewed the context if necessary. Reports that were not written in English were excluded from the study. Sixteen cases were identified that specifically described thymic carcinoma and paraneoplastic autoimmune diseases.[9-23]

Results

Table 2 shows the previously reported cases of thymic carcinoma and paraneoplastic autoimmune disease. The median age of the reported 17 cases was 53 years (range: 11–69 years). Of note, in all but two cases (including our case), autoimmune diseases were either present before the diagnosis of the malignant disease or were diagnosed just before recurrence. Polymyositis was the most frequently reported paraneoplastic autoimmune disease associated with thymic carcinoma. Other diseases included dermatomyositis, systemic lupus erythematosus, thyroiditis, encephalitis, hepatitis, and Morvan's syndrome.

Table 1: Autoimmune profile

	ANA	Anti-dsDNA	P-ANCA	C-ANCA	Anti-RNP	Anti-SSA	Anti-SSB
Reference range	40X(-)	0-200 (IU/ml)	0-3.499 (IU/ml)	0-1.99(IU/ml)	<7 (U/ml)	<7 (U/ml)	<7 (U/ml)
Value	1: 640X speckled	152.7	0.6	0.4	0.87	0.53	2.33
	IgG anticardiolipin	**IgM anticardiolipin**	**Anti-Jo-1 antibody**	**Anti-SM**	**Anti-Scl-70**	**Anti-CENP**	
Reference range	<10 (GPL-U/ml)	<12.5 (MPL-U/ml)	<7 (U/ml)	<7 (U/ml)	<7 (U/ml)	<7 (U/ml)	
Value	1.83	10.19	0.69	1.6	0.7	0.56	

Table 2: Reported cases of thymic carcinoma with paraneoplastic autoimmune disease

n	Age/gender	Disease status	Histology	Time from cancer Dx	Diagnosis	Management	Reference
1	63/male	Metastatic, SD	Poorly differentiated Neuroendocrine differentiation	36 months	Scleroderma	Hydroxychloroquine, steroid, colchicine, and chemotherapy	Our case
2	53/female	Primary metastatic	NA	4 years, at recurrence	Scleroderma	Systemic chemotherapy	[9]
3	11/male	Masaoka stage III, LELC	LELC	At diagnosis	Systemic lupus erythematosus	Surgery, chemotherapy, RT	[10]
4	59/male	Resectable	Large and clear cell carcinoma	At diagnosis	Limbic encephalitis	Steroid, IVIg, operation of tumor, in remission	[11]
5	44/female	NA	NA	NA	Limbic encephalitis	IVIg, steroid, and resection of tumor	[12]
6	63/female	Masaoka stage III,	Poorly differentiated squamous cell carcinoma	At diagnosis	MCTD, Hashimoto's thyroiditis	Steroid, operation of tumor, and RT	[13]
7	53/male	Masaoka stage III	Squamous cell carcinoma	At diagnosis	Dermatomyositis	Cured by operation	[14]
8	66/male	Resectable	Mixed: squamous cell carcinoma, adenocarcinoma, and basaloid cell carcinoma	At diagnosis	Polymyositis	Resection of tumor and steroid	[15]
9	23/male	Primary Metastatic	LELC	At diagnosis	Polymyositis	IVIg, steroid, chemoradiation, chemotherapy, and OP	[4]
10	24/male	Primary metastatic	LELC	At diagnosis	Polymyositis	NA	[16]
11	66/male	Masaoka stage IVa	NA	24 months	Scleromyxedema	Topical steroid	[17]
12	69/male	Resectable	Squamous cell carcinoma	At diagnosis	Opsoclonus and cerebellar ataxia	Steroid and operation	[18]
13	32/male	Masaoka stage III	Poorly differentiated	At diagnosis	Stiff man syndrome	Baclofen, BZD, and operation of tumor	[19]
14	64/male	Masaoka stage-III	Squamous cell carcinoma	At diagnosis	Dermatomyositis	Prednisolone, azathioprine, operation of tumor, and remission	[20]
15	21/male	Masaoka stage IVA	NA	At diagnosis	AMPAR encephalitis	Steroid, IVIg, op, chemo, and RT of tumor	[21]
16	32/male	Recurrence and lung metastasis	NA	At recurrence	Autoimmune hepatitis	Steroid and systemic chemotherapy	[22]
17	52/female	Masaoka stage IVa	Well-differentiated	At diagnosis	SLE, Morvan's syndrome	Prednisone and hydroxychloroquine	[23]

LELC: Lymphoepithelioma-like carcinoma, NA: Not available, IVIg: Intravenous immunoglobulin, MCTD: Mixed connective tissue disease, RT: Radiation therapy

There was only one reported case of scleroderma, which was also treated in our facility.[9] Various different pathologies were associated with the autoimmune diseases.

The treatment usually included steroids, and immune modulators such as intravenous immunoglobulin or disease-modifying antirheumatic drugs (azathioprine and hydroxychloroquine) were also used in some cases. In some cases, the paraneoplastic autoimmune disease was successfully treated after curative resection of the primary tumor. In two of the reported cases, systemic therapy, either parenteral chemotherapy or oral metronomic therapy, successfully controlled the autoimmune disease.[9,22] Effective treatment of the underlying cancer appeared to successfully reverse the autoimmune process.

Discussion

Autoimmune diseases have been widely reported to be related to cancer. A patient with an autoimmune disease may develop malignancy secondary to (1) target tissue damage from the autoimmune disease, (2) cytotoxic therapies used to treat aggressive manifestations, or (3) as a consequence of a defective immune system that predisposes to the development of both cancer and autoimmunity.[24] On the other hand, a patient with cancer may also develop secondary autoimmune disorders. Autoimmune diseases may be a by-product of anticancer immunity, and they can also be induced by anticancer therapy including chemotherapeutic agents and checkpoint inhibitors.[25] Paraneoplastic autoimmunity is often

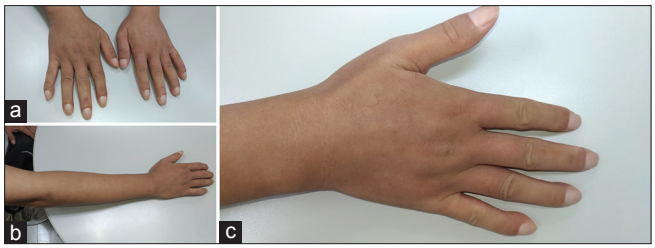

Figure 1: Typical presentation of systemic sclerosis in our patient including (a and b) Skin thickening of the fingers of both the hands, extending to near the elbow joint. This was sufficient for the diagnosis of systemic sclerosis according to the 2013 ACA/EULAR classification. (c) Sclerodactyly and puffy fingers were also evident

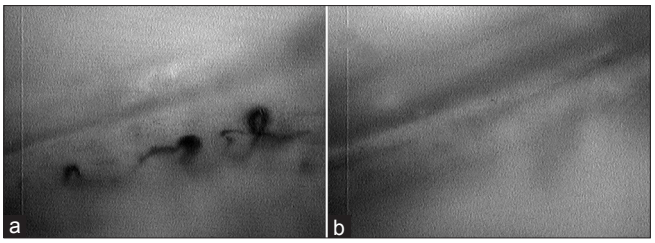

Figure 2: Nailfold capillaroscopy. Typical findings of nailfold capillaroscopy in systemic sclerosis patients including (a) bizarre capillaries and (b) loss of capillaries, as noted in our patient

more severe and often presents with a broader range of clinical signs and symptoms.[5]

Systemic sclerosis, also called scleroderma, is an autoimmune disease characterized by fibrosis of the skin, internal organs, and vasculopathy. This uncommon disease is associated with high rates of morbidity and mortality. Currently, the 2013 ACA/EULAR classification is used to make a diagnosis.[26] It can be classified into two major forms: the limited form and diffuse form. Some people have typical clinical features and autoantibodies but no skin involvement, and some have overlap syndromes with other autoimmune diseases. Typical autoantibodies include anti-centromere, anti-topoisomerase I, and anti-RNA polymerase III antibodies. No medication is known to alter the disease course, and the most important focus of therapy is on the treatment of major complications (interstitial lung disease, cardiac disease, pulmonary arterial hypertension, gastrointestinal dysmotility, renal crisis, and skin/musculoskeletal complications).[27,28]

Patients with scleroderma have an elevated risk of cancer, as indicated in two meta-analysis reports. The association is especially strong in lung, bladder, hematologic, liver, and nonmelanoma skin cancers.[29,30] Shah and Casciola-Rosen demonstrated that patients with RNA polymerase III autoantibodies have unique nucleolar expressions of RNA polymerase III in their cancerous cells, which are not detected in patients with other scleroderma autoantibodies or in normal control tissues. The authors indicated that autoimmunity may be a by-product of anticancer immunity and further postulated that occult tumors may exist which are eradicated by antitumor immunity. Consequently, they developed an algorithm for cancer screening in patients with systemic sclerosis.[25]

Thymic malignancy is associated with autoimmune diseases; however, the incidence of paraneoplastic autoimmune disease is far higher in thymoma than in thymic carcinoma. Approximately one-third of thymoma patients have been reported to have a paraneoplastic autoimmune syndrome, with the vast majority being myasthenia gravis. In one study, paraneoplastic autoimmune syndromes were associated with a younger age, female sex, thymoma histologic type, earlier stage, and a higher rate of total thymectomy and complete resection status. The relapse-free and overall survival rates are better in patients with paraneoplastic autoimmune syndrome, implying the existence of anticancer immunity.[7]

Several theories have been proposed to explain the link between thymic epithelial malignancy and autoimmunity, including the "escape theory," the "genetic theory," and the "autoimmune regulator (AIRE) theory." The "escape theory" states that in thymic malignancies where the tumor environment is disorganized, immature lymphocytes enter the affected site without passing through the thymic medulla, where self-tolerance is induced, resulting in autoimmunity. The "genetic theory" hypothesizes that genetic changes in neoplastic cells may impair normal T-cell development, thus generating self-reactive lymphocytes. The "AIRE theory" assumes that mutations of the AIRE gene, which encodes the protein that eliminates self-reactive T-cells, impairs the negative selection mechanisms of lymphocytes, and thus allows autoreactive T-cell to enter the target organ and induce autoimmunity.[5] However, these theories have yet to be validated, and further studies are warranted to explore the true mechanism.[2]

The management of paraneoplastic autoimmunity centers on treating the underlying malignancy. After successful chemotherapy or surgical excision of the tumor, subsequent improvements in autoimmunity are frequently noted. If anticancer therapy is difficult, immunosuppression is required to control the autoimmune disease. However, the clinical presentations of paraneoplastic immune-mediated diseases are often severe, and the treatment response is usually poor.[5] Moreover, immunosuppression may impair intrinsic antitumor immunity, causing a treatment dilemma.

With regard to our patient, the first-line treatment, which was given before the presentation of autoimmunity, was cisplatin with weekly infusions of high-dose 5-fluorouracil and leucovorin. This regimen is minimally toxic and has been shown to be beneficial in our facility previously.[9] After the first-line treatment, we gave him metronomic maintenance therapy, which has been shown to be effective against paraneoplastic autoimmune hepatitis.[22] After disease progression and the emergence of the autoimmune disorder, we started chemotherapy with the CAP regimen [doxorubicin (50 mg/m^2), cyclophosphamide (500 mg/m^2), and carboplatin (area under the curve = 3)], which is commonly used to treat thymic epithelial malignancies. Subjectively, his hand and

finger stiffness improved, which may have been secondary to the effect of immunosuppression or anticancer effect of the cytotoxic medication. The disease pace of thymic carcinoma was slow, which may have indicated robust anticancer immunity.

Conclusion

Thymic carcinoma with autoimmunity is rare, and the disease spectrum is broad. Although there is no consensus on optimal treatment options, treating the underlying malignancy is still the first priority. Reports on the most effective immune suppressive medication for paraneoplastic autoimmune disease are also lacking. A multidisciplinary approach may be needed to improve long-term outcomes.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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