Case Report
A rare thymoma case with seven paraneoplastic syndromes

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Received August 6, 2015; Accepted October 5, 2015; Epub October 15, 2015; Published October 30, 2015

Abstract: Thymoma is a kind of epithelial tumor of the thymus which about 30-50% patients accompanied by paraneoplastic disorders. However, the coexistence of seven symptoms in an individual is rare. This report represented a patient, diagnosed of thymoma, with myasthenia gravis, erythema multiforme, plasma cell cheilitis, recurrent oral ulcer, vitiligo, Raynaud’s phenomenon and fissured tongue. Detailed clinical manifestations, serum immune biomarkers, imaging study, electrophysiology examination and pathology results are described in this case.

Keywords: Thymoma, paraneoplastic syndromes, myasthenia gravis, erythema multiforme, plasma cell cheilitis, recurrent oral ulcer, vitiligo, Raynaud’s phenomenon, fissured tongue

Introduction
Thymoma refers to a kind of epithelial tumor of the thymus, which is commonly associated with paraneoplastic syndromes [1]. Paraneoplastic neurologic syndromes (PNS) constitute a rare entity of disorders, resulting from damage to the both central and peripheral nervous system, like limbic encephalitis, myasthenia gravis and Lambert-eaton myasthenic syndrome, unrelated to the tumor site [2]. PNS associated with thymoma is uncommon in the neurological settings and, in previous reports, occurred with only one and more infrequently of these manifestations simultaneously or sequentially in a single patient. Furthermore the symptoms of other diseases like dermatosis and rheumatism give much more difficulties to neurological physicians to make a comprehensive diagnosis in early-stage. Thus, a patient with thymoma who had as many as seven autoimmune disorders: myasthenia gravis, erythema multiforme, plasma cell cheilitis, recurrent oral ulcer, vitiligo, Raynaud’s phenomenon and fissured tongue is represented.

Case report
A 50-year old man was admitted to the department of neurology with a one-month history of progressive diplopia and left upper limb weakness. He also had a 2 years medical history of recurrent oral ulcers, lips swelling, skin lesions in trunk and extremities; fingers, genital and hair depigmentation. In the last 2 months, he lost 10 kg of weight. There were no other significant findings of family history.

On physical examination, bilateral hypophasis, etropion and left upper limb weakness with fatigue were evident. Mucosae of tongue, bucca and lips were eroded; tongue was fissured (Figure 1). Skin lesions in trunk and extremities appeared consistent with erythema multiforme (Figure 2). Distal fingers, toes and genital were depigmented (Figure 3). Nails looked brittle with longitudinal ridges; The skin of fingers turned pale, and became cold and numb when exposed to cold water (Figure 3).

Electromyography and nerve conduction studies were consistent with myasthenia gravis. Anti-acetylcholine receptor antibodies and Titin antibodies were positive with respective P/N value of 2.89 (b2.5) and 2.52 (b1.99), while PsmR antibody and RyR antibody were in normal range. All paraneoplastic biomarkers including Amphiphysin, Ri, Yo, Hu antibodies were negative, while CV2.1 antibody was positive. A computer tomography (CT) contrast scan
revealed an anterior mediastinal mass suggestive of thymoma (Figure 4). A lip biopsy showed histology consistent with plasma cells cheilitis.

Finally, this patient underwent a needle biopsy of thymoma. The pathology and immunohistochemical results showed that lymphocytes in tissue were originated from T-cells, TDT partly positive, Ki67: 70% positive. In the epithelial cells, p63, HCK and CK broad were positive, but TTF-1, SPA negative (Figure 5). The final result confirmed a WHO type B2 thymoma.

Considering that the mass was too big and close to large vessels, partly invasive to the lung, the patient was eventually suggested to accept radiotherapy and chemotherapy treatments.

Discussion

We present a patient with thymoma associated multiple paraneoplastic syndromes, including myasthenia gravis, erythema multiforme, plasma cell cheilitis, vitiligo, Raynaud’s phenome-
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All of the above symptoms may have been reported respectively, but rarely occur simultaneously or sequentially in a single person, and some of which were reported as paraneoplastic syndromes with other tumors. It has been 4 years before the finding of thymoma without any treatments, in this patient, which gave us a precious chance to observe more clinical symptoms occurred in this special case. Previously, one patient was reported with myasthenia gravis, ulcerative colitis, alopecia areata, vitiligo, and lichen planus, except the finding of any thymoma [3]; Another patient with thymoma accompanied by fewer symptoms including myasthenia gravis, alopecia areata, vitiligo and...
lichen planus [4]. Thus it could be the first report that paraneoplastic seven symptoms occurred in a single patient with thymoma.

Myasthenia gravis (MG) is one of the most common paraneoplastic syndromes accompanied by thymoma, meaning that almost 30-50% cases are linked to MG [5]. It is a heterogeneous neuromuscular junction disease characterized by muscular weakness and fatigability, mainly caused by antibodies against the acetylcholine receptor (AChR). When MG occurs along with a neoplasm, it turns out a paraneoplastic disease. Although the etiology of paraneoplastic MG is well known as an autoimmune reactive process, the antibodies in it probably indicate different clinical features. MG patients with RyR antibodies are characterized by frequent involvement of neck muscles at onset, and a more severe disease, while respiratory symptom is more typical in patients with titin antibodies. Absence of RyR antibodies, limb features are typical at onset. As reported, a majority of paraneoplastic MG patients have RyR antibodies, indicating that neck weakness and non-limb distribution of MG symptoms are initial characteristic features associated with paraneoplastic MG [6]. In this case, the patient

Figure 5. Immunohistochemical results showed that CD20 positive, TDT partly positive, Ki67 70% positive. In the epithelial cells, p63, HCK and CKs were positive (HE = Hematoxylin and eosin).
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has atypical initial features of diplopia and left upper limb, with no respiratory symptom, and has tintin antibodies, no RyR antibodies. It is distinct from most of other cases, while the underlying mechanism required further research.

Plasma cell cheilitis belongs to a heterogeneous group of rare dermatological diseases characterized by the infiltration of mature plasmocytes that affects skin or mucous membranes, especially areas of folds and the oral mucosa [7]. However, rare associations of plasma cell cheilitis and paraneoplastic syndrome, occurring in leukemia patients, have been described as isolated cases. To date, as far as we know, there was no such a case, one patient with thymoma and plasma cell cheilitis, until we reported. Although the etiology of this disease still remains unclear, in recent years, a possibility has been demonstrated that the influence of T cells and macrophages on cellular differentiation is closely related to the pathogenesis of plasma cell cheilitis [8]. Thus, in this case, as we assumed, the significant development of T cells may be a key for the presence of plasma cell cheilitis.

Vitiligo is a progressive depigmenting disorder characterized by the presence of white patches and hairs due to destruction of functional melanocytes in the epidermis. Although the pathogenesis remains obscure, recent studies indicated that cellular immunity plays an important role in the melanocyte damage and apoptosis process, which is closely in relation to occurrence and development of vitiligo [9]. In our case, the lower ratio of CD4+/CD8+ and higher level of CD8+ could be the cause of vitiligo. By far, case reports of thymoma-related vitiligo are peculiar, and of 98 subjects with thymoma, in a study, only 1.1% of those presented the manifestations of vitiligo [10]. In a most recent case report, a patient with thymoma had fewer symptoms like MG and vitiligo, and finally histology confirmed a type B2 thymoma, which was similar to the pathological type in our patient [4]. Thus, it is assumed that the coexistence of MG and type B2 thymoma may play a role in the presence of vitiligo, but the etiology need to be investigated in subsequent studies.

Erythema multiforme (EM) is a rare, acute and recurrent inflammatory disorder which affects skin or mucous membranes. The typical skin lesions appear individual lesions less than 3 cm diameter with a regular round shape, a well-defined border, and two concentric palpable edematous rings, paler than the centre disc, usually called “bulls eye” lesions. The mucosa including genital, oral and eyes, may be involved. EM is thought to be caused by a hypersensitivity reaction with the appearance of cytotoxic T lymphocytes in the epithelium inducing apoptosis in keratinocytes, which leads to satellite cell necrosis. EM can be triggered by a number of variants, but more than 90% of cases are associated with preceding infection with herpes simplex virus (HSV) [11]. Most other cases are in relation to a range of drugs, which have been identified in 59% of cases, while thymoma or other symptoms in this case have rarely documented association with EM [12]. In this case, excluding any forms of preceding infection or use of medication, it seems to be that thymoma triggered T-cell-mediated immune reaction to the precipitating agent, which leads to a cytotoxic immunological attack on skins of trunk and extremities and genital mucosa. Finally, as far as we know, it may be the first documented patient with EM, thymoma and other several symptoms, although the underlying reason has no answer yet.

Raynaud’s phenomenon (RP) is a disease due to recurrent, reversible vasospasms of small arteries and arterioles, involving usually the digital arteries in fingers and toes, triggered primarily by cold or emotional stress. Clinically RP is often recognized as a part of systemic sclerosis and characterized by the typical dual or tricolor changes in skin colour, affecting primarily acral body parts. They consist of sudden pallor of mostly single digit of fingers (white ischaemia), followed by reactive erythema (red hyperaemia) usually after rewarming. The occurrence of Raynaud’s phenomenon may be associated with neoplasm of the lungs, ovary, small intestine, breast, pancreas, kidney, lymphoma, plasmocytoma or leukemia, while the coexistence of thymoma and RP is rare [13]. In a case, RP improved after surgery in a patient with thymoma, but without any other symptoms [14]. In our cases, this patient has as many as 6 symptoms rather than thymoma and RP, which we have not known before. The etiology of Raynaud’s phenomenon in neoplastic diseases in unknown, it may be caused by para-
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Thymic syndrome paraproteins, cryoglobulins and certain cytokines [13]. Thus, it may be best explained by parathymic syndrome for the presence of RP, in our case, although it is difficult to confirm the truly causative relationships between them. As we proposed, thymoma may break the delicate balance between vasodilator and vasoconstrictor factors by immune-mediated, and to a certain extent, impact on the Raynaud’s phenomenon.

Recurrent oral ulcers are common inflammatory lesions of the oral mucous, usually round or ovoid, circumscribed by erythematous haloes with a yellow-grey floor and mostly painful. It often appears in Behcet’s disease and erythema multiform, but also could be a kind of paraneoplastic syndrome. According to the differential diagnosis from ulcers caused by Behcet’s disease or erythema multiform, we believed, thymoma could explain the presence of recurrent oral ulcers. As we know, no case reported the association of recurrent oral ulcer and thymoma, making the case a rare entity. Although we have no idea about the reason yet, the T-cell mediated immune response evoked by thymoma could play a key role in it.

Fissured tongue, also known as lingua franca or scrotal tongue, is characterized by the development of deep grooves or fissures on the dorsal and lateral surfaces of the tongue. Fissured tongue has an estimated prevalence of up to 20% in the general population and is more common in people with Down syndrome, Melkersson-Rosenthal syndrome, psoriasis, pernicious anemia, low serum levels of vitamin A, diabetes mellitus and certain autoimmune diseases [15]. As the etiology of fissured tongue remains obscure, we can not make sure whether this is a coincidental finding or a rare manifestation in this patient. However, it indicates a clue that fissured tongue may be an independent symptom of paraneoplastic syndromes with thymoma.

Conclusion

From the diagnostic impression of Behcet’s disease, to the diagnostic definition of thymoma with as many as seven disorders, this patient underwent a long and rough medical process, because it is too difficult to have a comprehensive awareness at the beginning. To our knowledge, there has been none similar report published yet. Tracing back the patient’s history, all the factors including the occupation, diet and living environment can not explain the diversities of his signs, compared to other patients with thymoma. Thus, we supposed that it may be attributed to genetic mutation or other cryptogenic causes, remaining to be confirmed by subsequent research.

There are also some limitations in our report. The paraneoplastic syndromes associated antibodies we investigated were currently known and common antibodies, but did not cover all the aspects of autoantibodies. Besides, no further investigation of genetic factors of the patient is another limitation for this case. Finally, the tumor is too large that surrounding the aorta to surgery, so, unfortunately, we could not observe the alterations of clinical symptoms after the thymoma resection.

Disclosure of conflict of interest

None.

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