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Quadruple overlapping autoimmune diseases manifested as sarcoidosis with mediastinal lymphadenopathy: A case report

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Abstract. We present a rare case of a 55-year-old female patient with quadruple overlapping autoimmune diseases, including vitiligo, autoimmune hypothyroidism, ulcerative colitis, and sarcoidosis with mediastinal lymphadenopathy. The patient had been suffering from vitiligo since 2003 and was diagnosed with autoimmune hypothyroidism and ulcerative colitis through thyroid ultrasound and colonoscopy, respectively. After physical examination, mediastinal lymph nodes enlargement was detected, and sarcoidosis was diagnosed through ultrasound bronchoscope-guided transbronchial needle aspiration (EBUS-TBNA), which is a quadruple overlapping sign of autoimmune disease of sarcoidosis that has not been reported previously. The patient was treated with oral Chinese medicine for leukoplakia, oral levothyroxine sodium tablets to control thyroid function, and Chinese medicine enema for colitis, with intermittent treatment for 2 years. Prednisone acetate was administered for 1 month to reduce the size of the enlarged lymph nodes. Our case highlights the importance of considering sarcoidosis as a potential diagnosis in patients with autoimmune diseases who present with mediastinal lymphadenopathy.

Key words: quadruple overlapping autoimmune diseases, vitiligo, autoimmune hypothyroidism, ulcerative colitis, sarcoidosis

Introduction

Sarcoidosis is a complex multi-system granulomatous disease of unknown origin that is characterized by non-caseating granulomas in affected organs, including the lungs, hilar lymph nodes, skin, and eyes (1). Sarcoidosis is a rare disease that is associated with immune abnormalities and is often found in patients with other autoimmune diseases, such as autoimmune thyroiditis, autoimmune hemolytic anemia, Sjogren's syndrome, idiopathic thrombocytopenic purpura, insulin-dependent diabetes mellitus, celiac disease, vitiligo, pernicious anemia, Addison's disease, and more. Sarcoidosis may be a unique cell-mediated autoimmune process (2). Here, we present a case of a patient who was diagnosed with sarcoidosis after experiencing mediastinal lymph node enlargement during a physical examination. In addition to sarcoidosis, the patient had a history of ulcerative colitis, vitiligo, and autoimmune thyroiditis, resulting in an autoimmune disease overlapping tetralogy of sarcoidosis, which has not been previously reported. We describe this unique case in detail below.

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Case report

A 55-year-old female teacher was found enlarged mediastinal lymph nodes without other respiratory symptoms in chest CT during her physical examination on April 9, 2000. The lymph nodes in the anterior trachea and posterior vena cava were approximately 12.5×6.0 cm in size, while those in the main pulmonary artery window measured approximately 12.2×7.6 cm (Figure 1A and 1B). Subsequent re-examinations on August 17, 2020 and December 20, 2020 showed no significant changes in lymph node size. However, on April 29, 2021, a marked increase in mediastinal lymph node size was observed, with the lymph node in the anterior trachea and posterior vena cava measuring approximately 16.8×12.4 cm and the lymph node in the main pulmonary artery window measuring approximately 22.3×12.4 cm (Figure 1C). The subcarinal lymph node was also significantly enlarged, measuring 38.3×17.0 cm (Figure 1D). Blood, urine, and stool routine tests, liver and kidney function tests, blood lipids, and tumor markers were all normal. C-reactive protein 3.7 mg/L (normal 0-5); erythrocyte sedimentation rate 25mm/h; negative ENA spectrum screening; negative vasculitis antibody; and no response to the tuberculin test. Transbronchial needle aspiration (EBUS-TBNA) guided by ultrasound bronchoscope endoscopy was performed. Negative result occurred in antacid bacilli smear, PAS and hexaamine silver staining. Immunohistochemistry assay result are as follow: AE1/AE3 (-), CD117 (-), CD5 (Lymphocyte +), Desmin (-), Ki67 (20%+), TdT (-). Pathology report showed non-caseating necrotic lesions, as shown in Figure 1E, that can be considered as sarcoidosis.

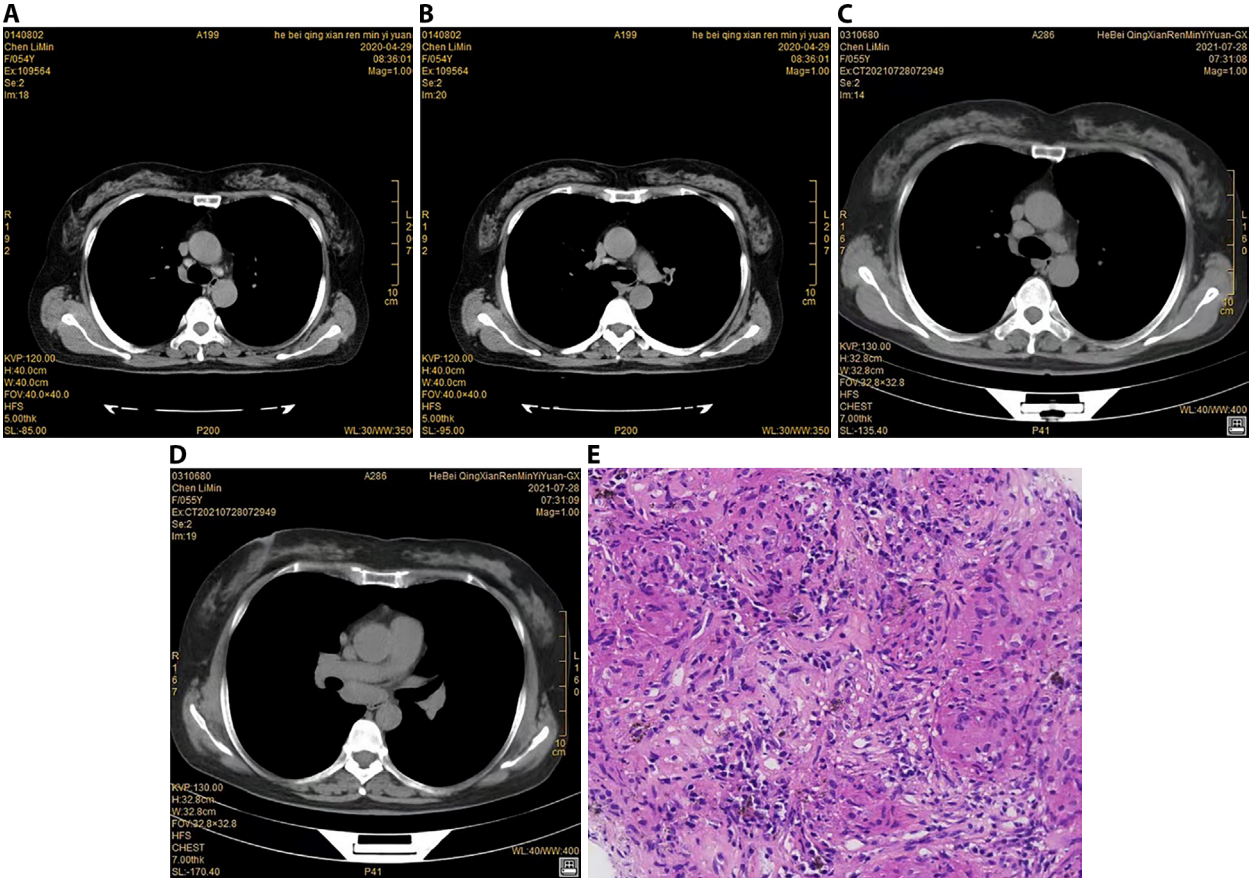

Figure 1. Chest CT and pathological pictures. (A) CT of the chest showed that the size of lymph nodes in the anterior trachea and posterior vena cava and main pulmonary artery window; (B) CT of the chest showed that the subcarinal lymph nodes enlargement was not obvious; (C) re-examination on Lymph nodes in the anterior trachea and posterior vena cava and main pulmonary artery window re-examination on subcarinal lymph nodes; (D) CT of the chest showed that the size of subcarinal lymph node; (E) Pathology report showed non-caseating necrotic lesions.

In addition, the patient has suffered from vitiligo since 2003, with multiple flaky leukoplakia on the skin of both hands. And leukoplakia appeared on the forehead skin in 2008. The leukoplakia on forehead skin subsided after the treatment of oral Chinese medicine, but the skin leukoplakia on the hands persisted (Figure 2). The patient has autoimmune hypothyroidism for 5to 6 years. The initial examinations of thyroid function are as following: TSH (serum thyrotropin) 16.4 mIU/L (normal 0.36~5.5), serum total T3 0.50 ng/dL (normal 0.61~1.81), serum total T4 3.82 μg/dL (normal 4.40~12.5), TpoAb (anti-thyroid peroxide antibody) greater than 1300 U/mL (normal 0~60), TG-Ab (thyroglobulin antibody) 394.40 U/mL (normal 0~60). Thyroid ultrasound indicates diffuse thyroid damage. The patient was diagnosed as autoimmune hypothyroidism, and took levothyroxine sodium tablets 50 μg once a day to control the situation. The patient had presented with abdominal pain, diarrhea, mucus, pus and blood in the stool 15 years ago, and diagnosed to be ulcerative colitis by colonoscopy and pathology analysis (Figure 3), sigmoid colon and rectum lesions became severe, taking oral Chinese medicine and Chinese medicine enema, intermittent treatment for 2 years to relieve the disease.

Sarcoidosis complicated with vitiligo, autoimmune thyroiditis, ulcerative colitis coexist as a tetralogy of overlapping signs. After the patient was told that he can continue to observe without medicine, the patient requested treatment and took prednisone 30 mg orally once a day. After treatment for one month, the mediastinal enlarged lymph nodes were smaller than before. Subsequent treatment is ongoing currently.

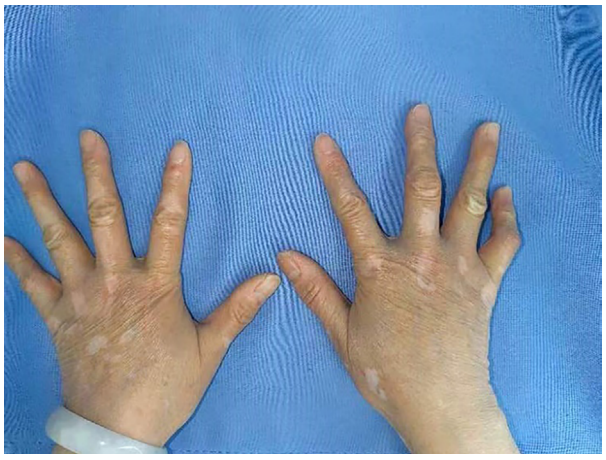

Figure 2. Mltiple flaky leukoplakia on the skin of both hands.

Discussion

The current case presented as sarcoidosis complicated with vitiligo, autoimmune thyroiditis, ulcerative colitis that coexisted as a tetralogy of overlapping signs. Clinically reported cases like this support a basic concept that common genetic and immunopathogenic theories linking sarcoidosis with other autoimmune phenomena are not just accidental associations. Fries et al.(3) reported 8 patients with sarcoidosis complications in Northern Europe out of 680 cases of ulcerative colitis, which is equivalent to 1 in 100,000.Out of 302105 patient who hospitalized for Inflammatory bowel disease (IBD), only 1495 patient was diagnosed with sarcoidosis with ulcerative colitis. The probability of simultaneous disease is less than 0.5%(4). Therefore, sarcoidosis with ulcerative colitis may not be accidental. Common factors for the two diseases remain to be discovered. According to a daily report, in a human leukocyte antigen typing of white people in Europe and the United States, 21% to 28% of healthy subjects and subjects with one of these two diseases had HLAD8 and DR3, while 3 out of 8 patients with ulcerative colitis and sarcoidosis (38%) had human leukocyte antigen-B8 and DR3. Patients who suffered ulcerative colitis with this human leukocyte antigen phenotype may be more likely to develop into sarcoidosis(5). Both vitiligo and autoimmune thyroiditis are a result of self-intolerance, which closely relate to the development of autoantibodies against thyreocytes and melanocytes. In cases of cluster autoimmunity, and vitiligo cases associated with sarcoidosis reported in the literature, sarcoidal lesions sporadically appeared on vitiligo macules(6). Our case is different from previous reports for enlarged mediastinal lymph nodes, with no nodules on the skin and no lesions in the lungs.

Sarcoidosis with mediastinal lymphadenopathy is mainly misdiagnosed as tuberculosis. Sarcoidosis and mediastinal lymph node tuberculosis are two granulomatous diseases. The distinction between these diseases depends on clinical manifestations and microbiology Mycobacterium tuberculosis Investigation, tuberculin skin test and cytopathological features of granuloma(7). Intrabronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA) is a commonly used method for the diagnosis of mediastinal lymphadenopathy. EBUS can not only sample lymph nodes, but also judge their

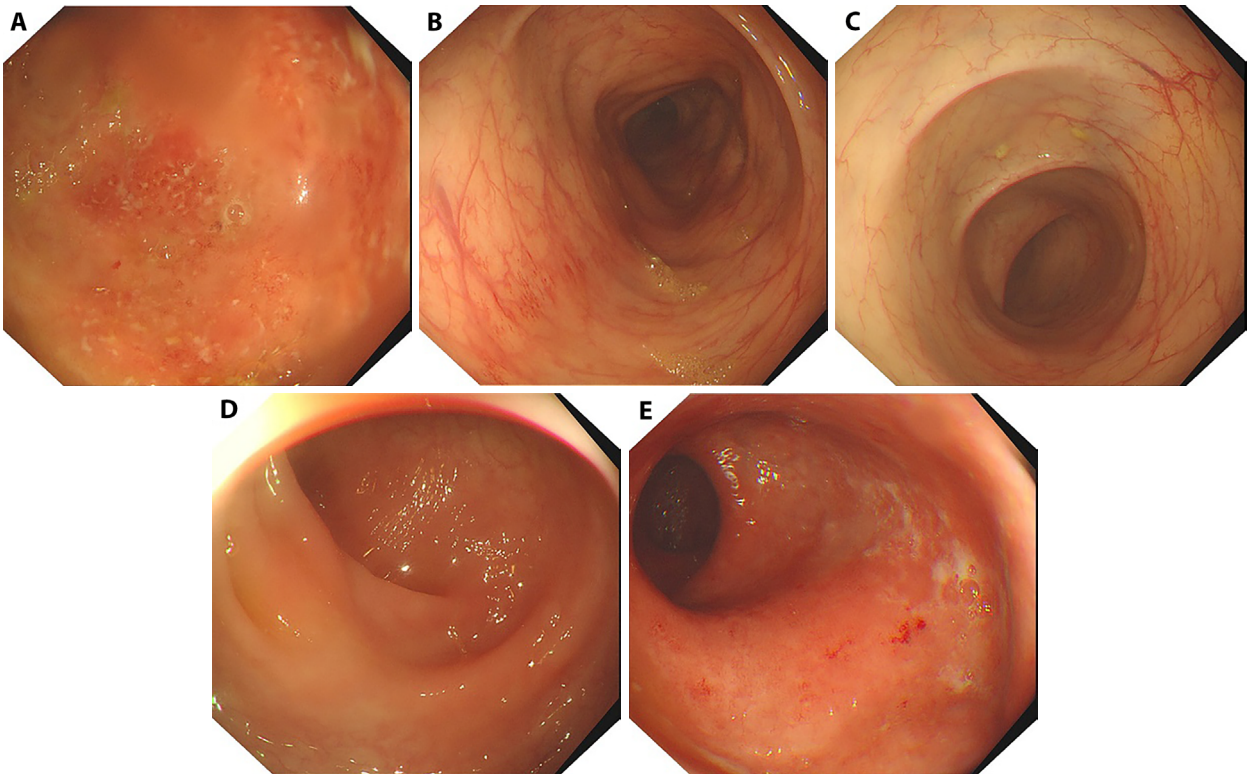

Figure 3. Result of colonoscopy. The appendix opening of ileocecal part is half moon shaped, and the ileocecal valve is lip shaped. (A) Normal in ascending colon, transverse colon, descending colon (B, C, D) Erosion of rectal mucosa with two purulent white moss (E)

possible diagnosis based on ultrasound images(8). Compared with tuberculosis, the angiogenesis of sarcoidosis is relatively increased(9). Clinical studies have found that the oval shape is relatively common in tuberculosis, while the swollen lymph nodes under the carina in our patient was oval. Uniform echo is more common in sarcoidosis. The presence of heterogeneous echo has a specificity, and 85.5% of it is used for the diagnosis of tuberculosis. Necrosis sign is helpful for the diagnosis of tuberculosis with high specificity and low sensitivity. But necrosis s needs to identify malignant lesions(10).

In addition to the biomarker ACE, elevated serum human chitotriosidase HC levels were proved to be a highly sensitive biomarker, especially suitable for the detection of systemic sarcoidosis. Elevated serum HC levels may suggest that patient's sarcoidosis may develop into lung disease(11). The sensitivity is estimated to be about 90%, which exceeds the sensitivity of the commonly used biomarker ACE by about 60%(12).

The pathological diagnosis of sarcoidosis is sometimes very difficult. Our patient was diagnosed after consultations with multiple pathologists. The findings under the electron microscope were studied. We found that multinuclear giant cells and epithelioid cells accounted for the majority in the diseased tissues(13). The increasing proportion of epithelioid cells; the abundant amount of rough endoplasmic reticulum and filled material that may be protein occurred in latter stage. The vitreous foramen of the lymph nodes begin around the granuloma. The capillaries in this region are surrounded by uniform lamellae, similar in structure to the basal lamella that next to the vascular endothelium. This area passes into a felt-like layer of delicate entangled filaments surrounded by a peripheral coat of collagenous fibres(14).

Conclusion

Therefore, for patients with autoimmune diseases, if mediastinal lymph nodes are found to be enlarged, the possibility of sarcoidosis must be considered. The diagnosis of sarcoidosis requires a combination of clinical, imaging, and pathology.

Conflict of Interest: The authors have no conflicts of interest to declare.

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