Revista Médica del
Hospital General de México

PERMANYER

Check for updates

CLINICAL CASES

Sarcoidosis: unusual presentations in a rare entity

Domingo Pérez-Bejarano

Ministry of Public Health and Social Welfare, Hospital General de Luque, Luque, Paraguay

Abstract

Sarcoidosis is a granulomatous inflammatory disease of unknown etiology that usually affects certain structures such as lungs, skin, eyes, liver, and lymph nodes. Three unusual clinical cases are illustrated and discussed in this paper: Hereford syndrome characterized by fever, anterior uveitis, and salivary gland hypertrophy in its incomplete form; the association of sarcoidosis with thymoma and myasthenia gravis as an expression of an autoimmune complex; and finally, pulmonary hypertension as an epiphenomenon to sarcoidosis, which showed a partial response to immunosuppressants. The reporting of the rare manifestations of this disease is meant to serve as a reminder that symptoms from various systems can come together to form a single diagnostic algorithm, and it also demonstrates the wide range of presentations that can be observed in clinical practice.

Keywords: *Sarcoidosis. Heerfordt's syndrome. Thymoma. Pulmonary hypertension.*

Introduction

Sarcoidosis is a systemic inflammatory disease whose pathological substrate is the formation of granulomas in several organs. It generally affects adults between 25 and 40 years of age and shows a higher incidence among Scandinavians and African-Americans. Their natural history is variable, and they may represent asymptomatic or self-limiting entities or manifest as chronic or rapidly progressive diseases[1].

Epidemiology, pathophysiology, diagnosis, and treatment

The annual incidence of sarcoidosis varies according to the region studied, with the highest rates in northern European countries (11-15/100,000) and the lowest in East Asian countries (0.5-1/100,000). The true epidemiological burden of the disease is unknown as even within countries they can vary. Thus, in the United States, it can be noted that the incidence among African-Americans is much higher than among Caucasians. The etiology of the disease is unknown and it is postulated that the interaction of a certain genetic terrain with environmental factors (antigens such as vimentin, bacterial or fungal particles, and even fragments of mycobacteria) could be the causal factors in the context of certain risk factors such as family history, smoking, occupational exposure, and obesity[2].

Although it can involve any organ, the lungs and lymph nodes are preferential sites (> 90%), followed by the skin (14-32%), eyes (8-20%), liver (11-18%), spleen (7-20%), joints (8-9%), heart (2-11%), and nervous system (2-7%). Regardless of the presence or absence of respiratory symptoms, nearly half of patients with sarcoidosis have extrapulmonary findings and diagnosis is usually made by biopsy of accessible affected tissues where sarcoid granulomas are described. A fundamental clinical gesture is the exclusion of other

Correspondence:
Domingo Pérez-Bejarano
E-mail: domineumo@yahoo.com

Date of reception: 01-03-2024
Date of acceptance: 14-10-2024
DOI: 10.24875/HGMX.24000017

Available online: 01-04-2025
Rev Med Hosp Gen Mex. 2025;88(4):217-222
www.hospitalgeneral.mx

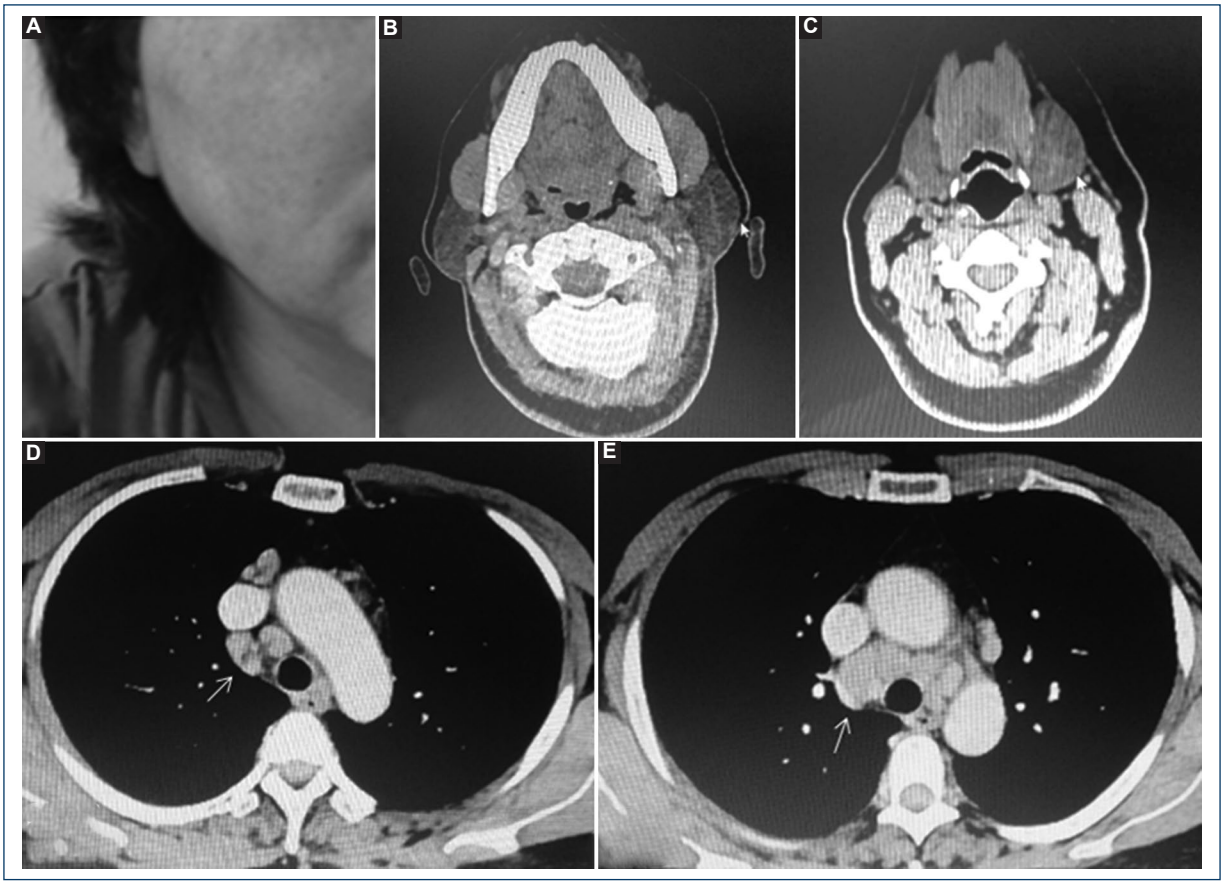

Figure 1. A: swelling of the right parotid region. **B:** computed tomography (CT) scan of the neck showing hypertrophy of both parotid glands. **C:** CT of the neck indicating hypertrophy of the submaxillary glands. **D:** CT of the chest (mediastinal window) in which right paratracheal nodes are indicated. **E:** CT of the chest showing retrocavoaortic and subaortic peritracheal mediastinal nodes.

granulomatous diseases, which is a high priority in regions where tuberculosis and some mycoses are endemic. The first line of treatment is usually corticosteroids, although in cases of therapeutic failure or involvement of certain organs, they are associated with immunosuppressants and/or biological agents[3].

Considering the less frequent manifestations of sarcoidosis is relevant, as they have a significant burden of relative morbidity and mortality. In this report, we present three clinical cases of sarcoidosis of unusual presentation seen in a referral hospital in our country and that have little reference in the Hispanic medical literature.

Presentation of cases

Case 1

A 53-year-old female healthcare provider, non-smoker with no comorbidities, presented with a 3-week history of conjunctival irritation with a feeling of dry eyes and dark spots in bilateral vision accompanied by bilateral and progressive swelling of the parotid and submaxillary regions. A week earlier, she reported intermittent palpitations and shortness of breath accompanied by feverish sensations. Vital signs: heart rate 88 × min, respiratory rate 20 × min, axillary temperature 37.5°C, oxygen saturation 94% at room air. Physical examination revealed moderate swelling of parotid and submaxillary regions (Fig. 1A-C), with no palpable peripheral lymphadenopathy and no signs of paresis or facial paralysis. Normal blood count, erythrocyte sedimentation 1 h: 24 mm, C-reactive protein 10 mg%, anti-nuclear antibody + (1/80), negative rheumatoid factor, human immunodeficiency virus (–), immunoglobulin M antibodies to Epstein–Barr virus, toxoplasmosis, rubella and cytomegalovirus (–), β-2 microglobulin 2.14 mg% (normal < 3 mg/dL), PPD 0 mm. In view of the findings of chest computed tomography (CT) scan

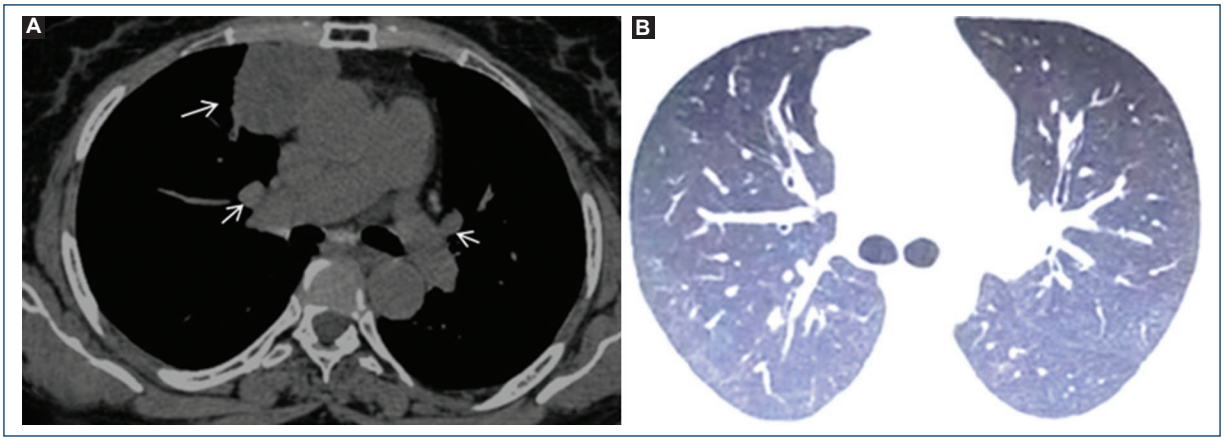

Figure 2. A: CT scan (mediastinal window) denoting mass in the anterior mediastinum (long arrow) and some adenomegaly (short arrows). **B:** high-resolution CT scan of the chest (pulmonary window) showing confluent subpleural nodular opacities in the right posterior region and slightly more scattered in the left lung.

(Fig. 1D and E), mediastinoscopy and lymph node biopsy are suggested. The pathological report mentions a chronic granulomatous inflammatory process with negative stains for acid–fast bacillus and fungal elements, compatible with sarcoidosis. The diagnosis is incomplete Heerfordt syndrome, with a good evolution after oral treatment and decreasing with prednisone (50 mg) for 12 months. After 4 years of follow-up, no recurrence was reported.

Case 2

A 34-year-old male was a non-smoker with a history of hospitalization in the intensive care unit due to severe COVID-19 6 months before the consultation and whose routine check-ups detected an anterior mediastinal mass and mediastinal and supraclavicular polyadenopathy (Fig. 2). Weeks after the second dose of ChAdOx1, he presented regurgitation of fluids through the nose, with fatigue of the oral and facial muscles plus swallowing disorders without weakness of limbs. Electroneuromyography confirms a pattern of post-synaptic neuromuscular plaque and mild positive repetitive stimulation (discrete polyneuropathy to axonal motor predominance). Elevated levels (5.85 nmoL/L) of anti-acetylcholine receptor antibody by radioimmunoassay (normal value < 0.05 nmoL/L) were noted. Biopsy of two right supraclavicular nodes showed extensive granulomatous lymphadenitis with no evidence of microorganisms or proliferative process, suggestive of sarcoidosis. Subsequent excision of the mediastinal mass allows its pathological classification as thymoma, subtype 2. Neurological symptoms improve and lymph nodes decrease considerably in size after multidisciplinary management (cisplatin-based chemotherapy, radiotherapy, and prednisone 50 mg). The proposed single diagnosis was thymoma, sarcoidosis, and myasthenia gravis. At 3-year follow-up, he showed a good clinical evolution.

Case 3

A 59-year-old woman was a long-term hypertensive, non-smoker, who consulted for slowly progressive dyspnea of 10 years of evolution that is made with slight exertion in the past 3 months, drumstick fingers, basal bilateral crackles. Known diagnosis of sarcoidosis by transbronchial biopsy, 2 years before consultation and history of treatment with prednisone for a short time. Heart rate 98 × min, respiratory rate 28 × min, blood pressure 100/70 mmHg, O_2 saturation: 92% (FiO_2: 21%). Chest X-ray: basal bilateral reticulonodular opacities. Chest CT: bilateral panalization (Fig. 3), spirometry shows forced vital capacity of 70% of the predicted (Hankinson), paO_2: 62.5 mmHg, echocardiography that reports significant elevation of estimated pulmonary artery systolic pressure (PSAP) (61 mmHg and 81 mmHg), mild left ventricular hypertrophy and left ventricular ejection fraction: 74%, ergometry: negative for ischemia, Doppler ultrasound of the lower limbs without signs of deep vein thrombosis, D-dimer within normal values. The proposed diagnosis was stage IV sarcoidosis (Scadding) and pulmonary hypertension (PH). Azathioprine (50 mg/d) and prednisone (20 mg/d)

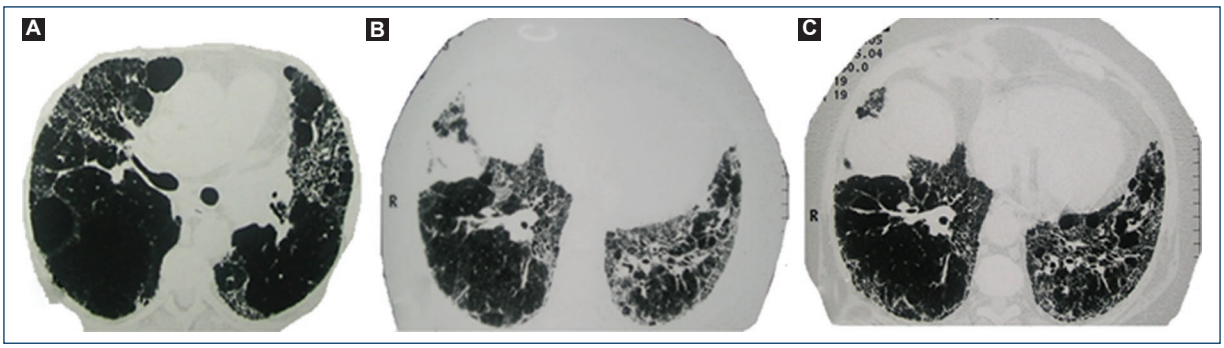

Figure 3. A: CT scan of the thorax where the considerable caliber of the right branch of the pulmonary artery in relation to the aorta can be observed. **B:** CT scan of fine sections of the chest that in lower regions shows areas of parenchymal distortion, areas of normal structure, and patched areas of ground glass. There are traction bronchiectasis and areas of peripheral panalization, insinuating, however, a peribronchial predominance of opacities. **C:** chest CT performed 9 months after immunosuppressive treatment, in which an apparent improvement of the ground glass pattern is observed, but an aspect that should be interpreted with caution since the techniques used for CT are clearly different.

were initiated at the request of the patient and as compassionate therapy. Six months later, he reported a marked improvement in dyspnea without objective changes in the control tomography. Follow-up echocardiography reports PSAP: 25 mmHg, EF: 70%. The patient remains stable for three more months and then decides to abandon treatment, seeing in weeks a new progressive worsening until dyspnea at rest.

Discussion

The wide range of clinical-pathological presentations of sarcoidosis has justified the nickname of "great imitator." Less frequent forms (1-5%) include involvement of the salivary glands, bones, bone marrow, gastrointestinal tract, and upper airways[4]. In relation to the cases presented here, there are only 111 reports of sarcoidosis associated with PH, 74 cases of Heerdfort syndrome, and only 1 case report of thymoma and myasthenia gravis associated with sarcoidosis in two reference databases (PUBMED and Lilacs).

The analysis of five cases of uveoparotid fever (Heerfordt, 1909) associated with neurological symptoms resulted in the proposal of a different manifestation of sarcoidosis by Jan Waldestrom in his original article of 1937[5]. Heerfordt–Waldestrom syndrome is considered complete when it shows all four main symptoms (fever, anterior uveitis, parotid and/or salivary gland hypertrophy, and facial paralysis) or incomplete when it shows two of the following: anterior uveitis, parotid hypertrophy, and facial paralysis[6,7]. The first case, illustrated in this essay, presented the incomplete form of this entity, but as a manifestation of a systemic involvement, proven by the results of mediastinoscopy. The presence of facial paralysis in this syndrome has an incidence of approximately 25-50% and the complete form constitutes only 0.3% of all cases of sarcoidosis[8,9]. Ocular manifestations represent the most common symptom of the syndrome. In a capital series of 83 patients, Darlington et al. found that 84.5% of ocular sarcoidosis cases develop lymphadenopathic hypertrophy and pulmonary infiltrates at a 2-year follow-up. A useful clinical fact is that in 40% extrapulmonary manifestations (skin lesions, cranial nerve palsy, or hypercalcemia) can be seen. It is interesting to note that although pulmonary involvement is not described as part of the syndrome, it can occur in up to 81% of cases. The diagnosis is clinical and is supported by histopathological findings (biopsy of lymph nodes, salivary glands, skin, or lungs)[10]. Heerfordt syndrome responds quite well to corticosteroid therapy and, as seen in the evolution of the case reported here, which was very favorable at 4 years of follow-up.

The second clinical case of this work illustrates the finding of a mediastinal mass in the context of a polyadenopathic syndrome that develops myasthenia gravis with bulbar involvement. Thymoma accounts for 90% of thymic neoplasms and is one of the most common tumors in the anterior mediastinum; however, metastases in regional nodes are not common. A systematic review has described lymphatic involvement in 3.3%, compared with 18.6% in thymic carcinoma and 28% in neuroendocrine thymic tumors[11]. The histopathological report of sarcoidosis in lymph node biopsy as a

comorbidity is an exceptional finding and, surprisingly, a case of regression of skin and lung lesions associated with sarcoidosis after thymectomy is reported[12,13]. It is appropriate, however, to point out many conditions that can be mimicked as sarcoidosis-like granulomatous reactions (infections, neoplasms, vasculitis, and inflammatory responses to environmental and occupational exposure). Some idiopathic inflammatory responses such as (granulomatous lesions of unknown significance syndrome), granulomatous interstitial lung disease related to common variable immunodeficiency, and necrotizing sarcoid granulomatosis are also cited as differentials. Taking into account this battery of differentials, it is understandable what Judson writes as the introduction to his publication: "*the diagnosis of sarcoidosis is arbitrary, not standardized and is never completely certain*"[14].

The neuromuscular involvement of the patient presented here stands out. Myasthenia gravis is the most prevalent paraneoplastic syndrome in the context of autoimmune dysregulation that induces thymoma as certified in a systematic review by Blum et al., who found a relative frequency of 63% in 507 patients operated on for the tumor. Dozens of other autoimmune entities with varied organ and system involvement are also cited[15]. Although it may be a simple coincidence or a real association, the medical literature suggests a bidirectional relationship between sarcoidosis and myasthenia gravis[16,17]. Sawada et al. describe a case of rheumatoid arthritis and sarcoidosis that develops neuromuscular symptoms, reflecting in the discussion 19 cases of sequential sarcoidosis to myasthenia gravis, 6 of them associated with thymic hyperplasia (4 cases) or thymoma (2 cases)[18]. The effects of rain depend on its intensity and also on the soil it wets. Why think of a sequential appearance of isolated diseases and not interpret them as an expression of the same substrate? Like Spinoza's God. In the case described here, the hypothesis of the cluster of entities resulting from an autoimmune flow is very seductive in noting that the neurological symptoms continue shortly after immunization without necessarily having a causal relationship, a phenomenon that meets the criteria of autoimmune syndrome after COVID-19 vaccine or generically: autoimmune/inflammatory syndrome by adjuvant[19]. Total resolution of symptoms after thymectomy and multimodal treatment also supports the theory. An updated review of the immunological mechanisms underlying sarcoidosis was recently published[20].

The third case described in this study deals with the association of sarcoidosis and PH. The overall prevalence of sarcoidosis in patients with sarcoidosis is 2.9-20% and entails significant morbidity and mortality, and it should be considered that multiple factors can contribute to its development: pulmonary parenchymal involvement, left ventricular dysfunction, veno-occlusive disease, thromboembolic phenomena, extrinsic vascular compression, granulomatous vascular inflammation, and sleep apnea, among others[21]. The gold standard for diagnosis is right cardiac catheterization which establishes PH when the PSAP > 20 mmHg[22], but screening should be initiated with transthoracic echocardiography when one of the following variables is found: persistent dyspnea despite treatment, when there are clinical signs of right ventricular failure, significant functional compromise (< 300 m walked or drop in saturation > 5% in the 6-min walk test), high levels of BNP, if > 20% pulmonary fibrosis is found on CT scan, increased ratio between pulmonary artery diameter and aorta or other signs of PH, decrease of > 15% in DLCO[23]. Hemodynamic study rooms are scarce in public health services in Paraguay, so sometimes a complete approach is not given, as in the case presented here.

The clinical response of the patient during the course of treatment with immunosuppressants was striking. There is currently no specific treatment for PH in sarcoidosis, although it is suggested that a multidisciplinary team evaluates on a case-by-case basis. Cases of hemodynamic response to treatment with corticosteroids or immunosuppressants are reported, although lines of research are preferentially aimed at vasodilators, which positively changed the history and prognosis of other forms of PH[24,25]. When the disease is very advanced, the option would be lung transplantation. This procedure has never been performed in Paraguay and there are currently no immediate plans.

Conclusion

This paper describes three clinical cases of infrequent forms of presentation of sarcoidosis (Heerdfordt syndrome, association with PH, and association with thymoma), seen in a public health hospital in Paraguay, together with a brief analysis of the relevant literature.

Funding

The authors declare that they have not received funding.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

References

1. Sève P, Pacheco Y, Durupt F, Jamilloux Y, Gerfaud-Valentin M, Isaac S, et al. Sarcoidosis: a clinical overview from symptoms to diagnosis. Cells. 2021;10:766.
2. Rossides M, Darlington P, Kullberg S, Arkema EV. Sarcoidosis: epidemiology and clinical insights. J Intern Med. 2023;293:668-80.
3. Neves FS, Pereira IA, Sztajnbok F, Neto NS. Sarcoidosis: a general overview. Adv Rheumatol. 2024;64:57.
4. Franzen DP, Brutsche M, Nilsson J, Böni C, Daccord C, Distler O, et al. Sarcoidosis - a multisystem disease. Swiss Med Wkly. 2022;152:w30049.
5. Waldenstrom J. Some observations on uveoparotitis and allied conditions with special reference to the symptoms from the nervous system. Acta Med Scand. 1937;91:53-68.
6. Fraga RC, Kakizaki P, Valente NYS, Portocarrero LKL, Teixeira MFS, Senise PF. Do you know this syndrome? Heerfordt-Waldenström syndrome. An Bras Dermatol. 2017;92(4):571-2.
7. Fujiwara K, Furuta Y, Fukuda S. Two cases of heerfordt's syndrome: a rare manifestation of sarcoidosis. Case Rep Otolaryngol. 2016;2026:3642735.
8. Makimoto G, Kawakado K, Nakanishi M, Tamura T, Noda M, Makimoto S, et al. Heerfordt's syndrome associated with trigeminal nerve palsy and reversed halo sign. Intern Med. 2021;60:1747-52.
9. Mikulic S, Patel P, Sheffield S, Kandah F, Velarde G. Heerfordt-waldenström syndrome manifesting as cardiac sarcoidosis. Cureus. 2020;12:e10619.
10. Darlington P, Tallstedt L, Padyukov L, Kockum I, Cederlund K, Eklund A, et al. HLA-DRB1* alleles and symptoms associated with Heerfordt's syndrome in sarcoidosis. Eur Respir J. 2011;38:1151-7.
11. Brascia D, De Palma A, Schiavone M, De Iaco G, Signore F, Panza T, et al. Lymph nodes involvement and lymphadenectomy in thymic tumors: tentative answers for unsolved questions. Cancers (Basel). 2021;13:5085.
12. Hato T, Yamaguchi M, Sugiyama A, Aoki K, Inoue Y, Fukuda H, et al. Hatched "egg" of thymoma with sarcoidosis. World J Surg Oncol. 2019;17:151.
13. Esendagli D, Koksal D, Emri S. Recovery of pulmonary and skin lesions of sarcoidosis after thymectomy. Acta Clin Belg. 2016;71:441-3.
14. Judson MA. Granulomatous sarcoidosis mimics. Front Med (Lausanne). 2021;8:680989.
15. Blum TG, Misch D, Kollmeier J, Thiel S, Bauer TT. Autoimmune disorders and paraneoplastic syndromes in thymoma. J Thorac Dis. 2020;12:7571-90.
16. Rizzi L, Sabbà C, Suppressa P. Sarcoidosis and autoimmunity: in the depth of a complex relationship. Front Med (Lausanne). 2022;9:991394.
17. Murphy MJ, Edemobi P, Leasure AC, Gulati M, Miller EJ, Damsky W, et al. Autoimmune comorbidities associated with sarcoidosis: a case-control study in the all of us research program. Rheumatol Adv Pract. 2023;7:rkad030.
18. Sawada J, Asanome A, Endo H, Saito T, Katayama T, Hasebe N. A case of myasthenia gravis following sarcoidosis and rheumatoid arthritis. Rinsho Shinkeigaku. 2013;53:351-5.
19. Jara LJ, Vera-Lastra O, Mahroum N, Pineda C, Shoenfeld Y. Autoimmune post-COVID vaccine syndromes: does the spectrum of autoimmune/inflammatory syndrome expand? Clin Rheumatol. 2022;41:1603-9.
20. Weeratunga P, Moller DR, Ho LP. Immune mechanisms of granuloma formation in sarcoidosis and tuberculosis. J Clin Invest. 2024;134:e175264.
21. Liu A, Price LC, Sharma R, Wells AU, Kouranos V. Sarcoidosis associated pulmonary hypertension. Biomedicines. 2024;12:177.
22. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RM, Brida M, et al. 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2022;43:3618-731.
23. Savale L, Huitema M, Shlobin O, Kouranos V, Nathan SD, Nunes H, et al. WASOG statement on the diagnosis and management of sarcoidosis-associated pulmonary hypertension. Eur Respir Rev. 2022;31:210165.
24. Israël-Biet D, Pastré J, Nunes H. Sarcoidosis-associated pulmonary hypertension. J Clin Med. 2024;13:2054.
25. Tana C, Drent M, Nunes H, Kouranos V, Cinetto F, Jessurun NT, et al. Comorbidities of sarcoidosis. Ann Med. 2022;54:1014-35.