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Case Report

Recurrent Heerfordt-Waldenström Syndrome with thyroid and meningeal involvement in a Chinese woman

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ABSTRACT

Sarcoidosis is a multisystem granulomatous disorder of unknown etiology, manifesting with bilateral hilar adenopathy, pulmonary reticular opacities, skin, joint or eye lesions. Heerfordt-Waldenström Syndrome – a constellation of facial palsy, fever, uveitis and parotitis – is a rare presentation of this disorder.

A 47-year-old Chinese woman presented with unintentional weight loss, lethargy with mediastinal and hilar lymphadenopathy. Biopsy of the right paratracheal lymph node via mediastinoscopy showed mycobacterial granulomatous lymphadenitis consistent with tuberculosis with several acid-fast bacilli identified. Lymphoproliferative disorder was ruled out.

She was started on treatment for tuberculosis. Eleven weeks into treatment, she developed a right facial palsy accompanied with fever, uveitis and occipital headache. At this juncture, further history revealed a background of recurrent alternating facial palsy and parotid gland enlargement which was treated for Bell's palsy by three different doctors. New nodules appeared in the left lobe of the thyroid gland. Biopsy of a palpable thyroid nodule and a right supraclavicular lymph nodule showed histological features suggestive of sarcoidosis. Fungal and mycobacterial infections were ruled out. In addition, examination of her cerebral spinal fluid showed lymphocytic inflammation. The serum ACE level was not raised.

A diagnosis of sarcoidosis with incomplete features of Heerfordt-Waldenström Syndrome along with thyroid and meningeal involvement was made. The patient was commenced on prednisolone and azathioprine and her symptoms responded shortly after.

We present a rare case of Heerfordt-Waldenström Syndrome with thyroid and meningeal involvement in a Chinese woman.

1. Introduction

Sarcoidosis is a multisystem granulomatous disorder of unknown etiology. It is characterized by the presence of non-caseating granulomas in the involved organs. It is most common amongst Scandinavians, African-Americans and Afro-Caribbean. The disease usually begins in the lung, skin or lymph nodes. Involvement in the other organs is less common. However, any organ can be affected. Pulmonary sarcoidosis is by far the most common involvement, with 90% of cases.

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A few clinical presentations are felt to be sufficiently diagnostic for sarcoidosis that a biopsy is not necessary. These presentations include Löfgren Syndrome (erythema nodosum, hilar adenopathy, migratory polyarthralgia and fever), Heerfordt-Waldenström Syndrome (facial palsy, fever, uveitis and parotitis) and asymptomatic bilateral hilar adenopathy [1]. Other than these, the diagnosis of sarcoidosis requires step-wise approach to identify organs affected and are amenable to biopsy. It should demonstrate non-caseating granulomas with exclusion of other causes of granulomatous disease such as mycobacterial and fungal infection.

A rare case of incomplete Heerfordt-Waldenström Syndrome with thyroid and meningeal involvement in a Chinese woman will be presented.

2. Case report

A 47-year-old Chinese woman presented with nine-kilogram weight loss associated with loss of appetite, lethargy and numbness of her limbs for seven months. She developed a non-pruritic maculopapular rash on both lower limbs one month prior to the consultation. As advised by her Traditional Chinese Medicine Physician, she consulted a cardiologist in February 2020.

Her electrocardiogram showed a right bundle branch block and her 2-D echocardiogram was normal. However, the chest x-ray revealed widening of superior mediastinum and bilateral hilar enlargement suggestive of mediastinal and hilar lymphadenopathy [Fig. 1A]. CT Scan of thorax confirmed the lymphadenopathy. The right paratracheal adenopathy measured 3.3×2.8 cm, right hilar adenopathy 3.5×2.3 cm, subcarinal adenopathy 4.5×1.7 cm [Fig. 2A and B]. There was no pleural or pericardial effusion. Cardiac chambers and major mediastinal vasculature were normal. There was a few subpleural nodules more on the right lung, along the oblique fissure. Otherwise, there was no pulmonary issue [Fig. 3A and B].

In light of the possibility of a lymphoproliferative disorder, she was referred to an oncologist. Positron emission tomography (Pet) scan body in early February demonstrated multiple F-fluorodeoxyglucose (FDG) avid cervical, thoracic and upper abdominal lymph nodes with standard uptake value (SUV) 2.4–26.5. Intense FDG uptake was seen in the bilateral parotid glands (SUV 11) and left submandibular gland (SUV 4). Several sub-centimeters subpleural nodules found in both lungs were not FDG avid. There was no FDG activity in the thyroid and heart. Overall, the Pet scan was suggestive of lymphoma [Fig. 4].

She underwent mediastinoscopy in mid-February 2020 for biopsy of the right paratracheal lymph node. Histology showed non-necrotizing granulomatous lymphadenitis in keeping with granulomatous inflammation and there was no evidence of lymphoproliferative disease. However, some rare granulomas with caseation were found. Several acid-fast bacilli were identified as well. Fungal stains were negative. The impression was mycobacterial granulomatous lymphadenitis consistent with tuberculosis. Culture for tuberculosis and TB PCR were unfortunately not sent. In view of the histological findings, she was started on treatment for tuberculosis. Tests for HIV and QuantiFERON TB gold plus were negative. She works as a cashier at a mini-supermarket and has no contact with birds and bats. A differential diagnosis of sarcoidosis was considered. Chest x-ray showed reduction in the size of hilar lymph nodes [Fig. 1B] within two months of treatment.

Eleven weeks into the treatment for tuberculosis, she presented with an acute right facial palsy in early May 2020. There was redness in both eyes and this was associated with blurring of vision. She had numbness of her soles, knee pain and occipital headache since late April 2020. She informed us then that she had similar right facial weakness seven months ago and this was associated with right parotid gland swelling. These were managed and resolved with a course of antibiotics from her family doctor. Another episode occurred a month later but with a left facial palsy and enlargement of both parotid glands. She consulted an otorhinolaryngologist. CT scan of parotids showed bilateral enlarged parotids, predominantly on the right, with inhomogeneous nodular enhancement in keeping with parotitis [Fig. 5A]. Fine needle aspiration of the parotid demonstrated inflammatory cells. Her complaints resolved with a course of prednisolone and Augmentin. The third episode with a left facial palsy and a swollen left parotid gland occurred in January

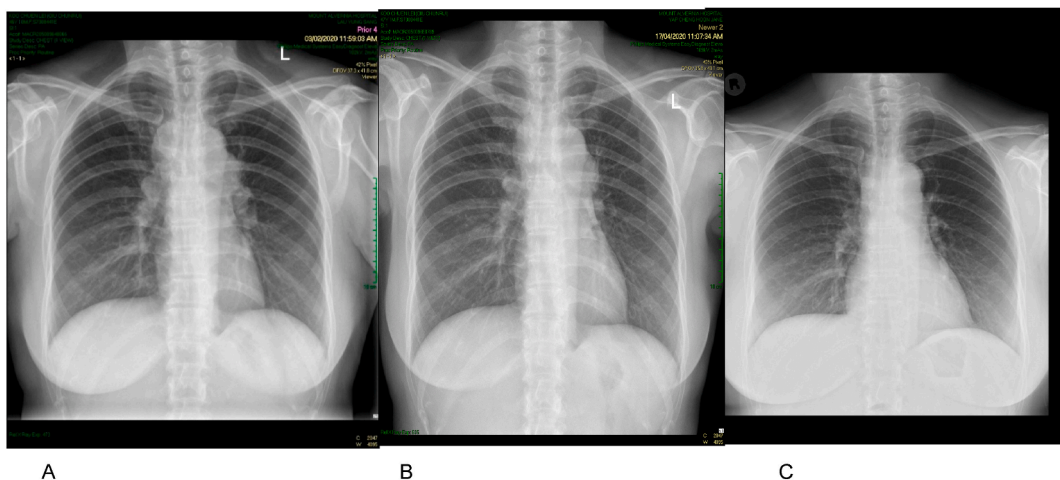


Fig. 1. (A) February 3, 2020 Chest X-Ray: Mediastinal and hilar lymphadenopathy. (B) April 17, 2020 Chest X-Ray: Reduction in the size of lymphadenopathy. (C) January 6, 2022 Chest X-Ray: Further reduction in the size of lymphadenopathy.

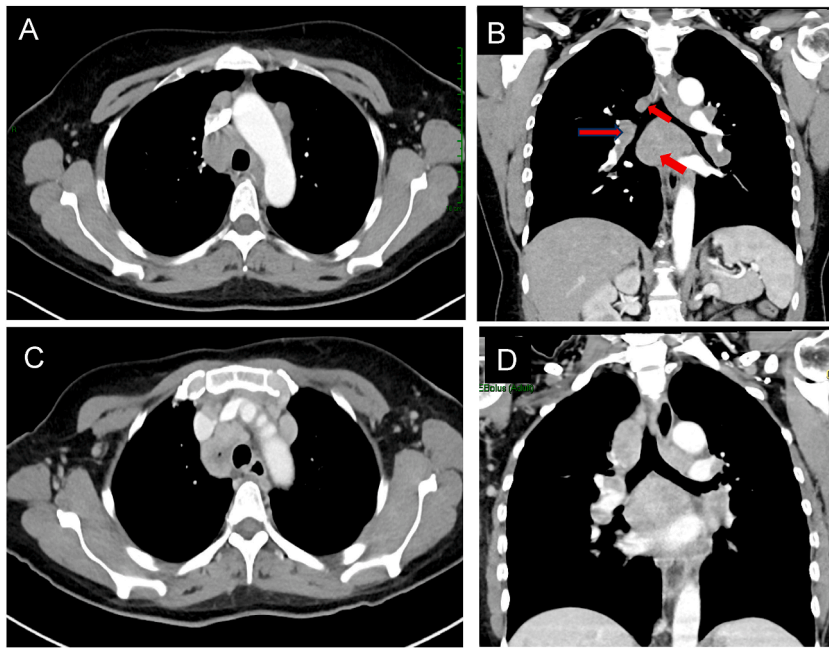


Fig. 2. (A) February 3, 2020 CT Thorax: Right paratracheal adenopathy, axial image. (B) February 3, 2020 CT Thorax: Right paratracheal, right hilar, subcarinal adenopathy (arrow), coronal image. (C) May 6, 2020 CT Thorax: Interval decrease in size of mediastinal nodes on CT with hypodense centres, axial image. (D) May 6, 2020 CT Thorax: Interval decrease in size of mediastinal nodes on CT with hypodense centres, coronal image. (A) and (B) The right paratracheal adenopathy measures 3.3×2.8 cm while the right hilar adenopathy measures 3.5×2.3 cm, subcarinal adenopathy measures 4.5×1.7 cm.

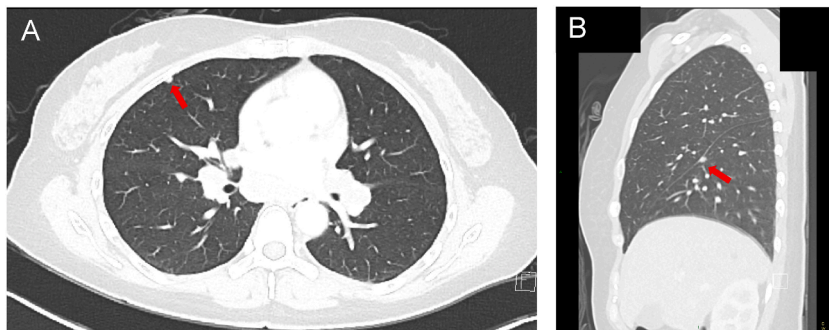


Fig. 3. (A) February 3, 2020 CT Thorax: Subpleural nodule (arrow), axial image. (B) February 3, 2020 CT Thorax: Right oblique fissure nodule (arrow), sagittal image.

2020. This time she consulted a doctor in a government hospital and was treated as Bell's palsy. During these three episodes, she did not experience any ocular symptoms or fever.

Patient further revealed that she had two transient episodes of left sided limb weakness a year ago. Her blood pressure was slightly raised. MRI brain showed left frontal development venous anomaly. There was no acute intracranial hemorrhage or infarct. MRA showed narrowing of proximal right external carotid artery. There was no significant stenosis of the internal carotid arteries, intracranial anterior or posterior circulation. The parotid glands were normal [Fig. 5B]. She was started on Adalat and Plavix for her hypertension and transient ischemic attacks.

When the fourth episode of facial palsy (right) occurred, she was admitted for investigations to confirm sarcoidosis with Heerfordt-Waldenström Syndrome, bilateral hilar and mediastinal lymphadenopathy, thyroid and neurological involvement. Clinical examination showed a right lower motor neuron facial palsy of House-Brackmann grade IV. Other neurological examination was unremarkable. The parotid glands were not enlarged. A left thyroid nodule was palpated. Her eyes were red and examination under slit lamp showed bilateral anterior uveitis, keratic precipitates on endothelial surface of cornea, mutton fat type which is typical of granulomatous uveitis [Fig. 6]. Of note, there was no hepatosplenomegaly and parotid gland enlargement in this episode. Low grade fever was documented.

Main otorhinolaryngological findings were acute sinusitis and laryngitis for which a course of Augmentin was started. Hearing tests showed bilateral mild to moderately severe sensorineural hearing loss, attributed to aging.

MRI brain did not show any meningeal and parenchymal enhancement. The parotids were not enlarged [Fig. 5C]. Lumbar puncture was carried out. The opening pressure was normal at 15 cm water. The CSF was clear and biochemistry was lymphocytic domi-

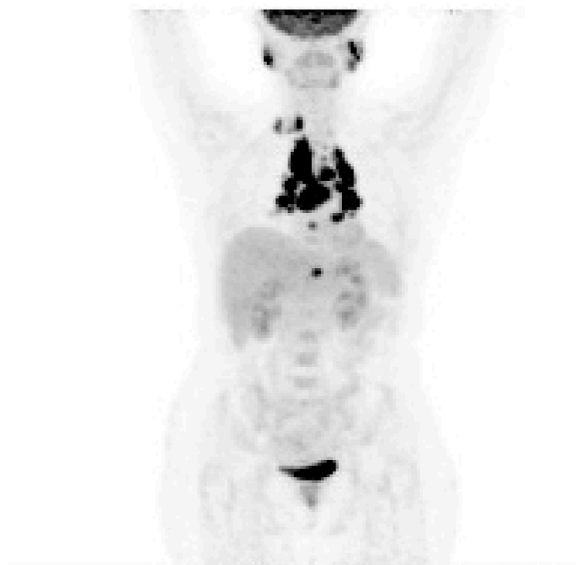


Fig. 4. February 5, 2020 PET Scan: Multiple F-fluorodeoxyglucose (FDG) avid cervical, thoracic and upper abdominal lymph nodes, with standard uptake value (SUV) 2.4–26.5. Intense FDG uptake was seen in the bilateral parotid glands (SUV 11) and left submandibular gland (SUV 4). No FDG activity in the thyroid and heart.

nant with no organism, acid fast bacilli and cryptococcus. *Mycobacterium Tuberculosis Complex* DNA was not detected. Cytology showed scattered small lymphocytes. No malignant cells were seen. Tetraplex PCR was negative for cytomegalovirus, herpes simplex virus, varicella zoster virus and *Toxoplasma gondii*. The culture for tuberculosis was negative. These findings were suggestive of meningeal involvement. Nerve conduction study did not show electrophysiological evidence of peripheral neuropathy.

CT scan of the thorax, abdomen and pelvis was done. This time the left thyroid gland was enlarged with multiple hypodense nodules and these were not present in the February scan [Fig. 7A and B]. The enlarged supraclavicular lymph nodes were stable in size since February 2020. There was a slight interval decrease in the size of some of the mediastinal lymph nodes. Some of the larger nodes had heterogenous hypodense centres suspicious of necrosis [Fig. 2C and D]. The enlarged pulmonary hilar lymph nodes also showed some reduction in size, the largest at left hilum measured 1.5 cm compared to 1.9 cm previously. The nonspecific subpleural pulmonary nodules were stable. Small hepatic cysts were detected in the right lobe of liver. No other abnormalities were detected in the abdomen. Ultrasound guided core biopsies of the left thyroid lobe nodule and right supraclavicular node were carried out. Both showed granulomatous inflammation [Fig. 8]. Acid fast bacilli, *Mycobacterium Tuberculosis complex* DNA and fungus were not detected. The cultures for tuberculosis and fungus were negative.

The treatment for tuberculosis and hypertension were continued. Atorvastatin was started for her hypercholesterolemia. She was given topical prednisolone forte for the uveitis and intravenous hydrocortisone 100 mg eight hourly, followed by prednisolone 30 mg om for the meningeal inflammation and facial palsy. Clinically she improved within 3 days. The eye redness resolved and her vision improved. Her numbness and giddiness likewise reduced. Azathioprine 75 mg om was added for the steroid sparing effect. Both medications were titrated over the months of treatment. The facial palsy improved from House-Brackmann grade IV to II. The palpable thyroid nodule had disappeared. The mediastinal and bilateral hilar lymphadenopathy shown considerable reduction in size [Fig. 1C] at the twentieth month of steroid and azathioprine treatment.

Table 1 shows her blood test results. The conversion of ANA and anti-DNA were attributed to be drug induced, most likely isoniazid as there were no other features of autoimmune disease. Repeated electrocardiogram showed right bundle branch block. Telemetry was normal and PET scan body in February did not show any FDG activity in the heart. There was no cardiac involvement.

3. Discussion

We report an interesting and rare case of sarcoidosis with extrapulmonary manifestations in a Chinese female. Her initial presentation was that of a recurrent incomplete Heerfordt-Waldenström Syndrome with alternating facial palsy. We were unable to confirm that there was no fever and uveitis during the first three episodes. The fourth episode of facial palsy was not associated with enlarged parotid gland. Heerfordt-Waldenström Syndrome is a rare presentation of sarcoidosis, occurring in 0.3% of the cases in the complete form [2,3]. However incomplete presentation can occur as in our case [4,5]. These variants account for 4.1%–5.6% of cases [6]. Her presentations were recurrent and the facial palsy was alternating between the two sides within ten months. This is an interesting manifestation and is unusual for Bell's Palsy, requiring a comprehensive investigation [7].

Ocular disease may be the initial manifestation in sarcoidosis involving 25–60% of patients with systemic sarcoidosis [8]. The most common manifestation is uveitis accounting for 30–70%. It is a frequent and early feature of sarcoidosis. More than 80% of uveitis cases manifested before or within one year after the onset of systemic disease. Anterior uveitis is more common, 70%–75% of

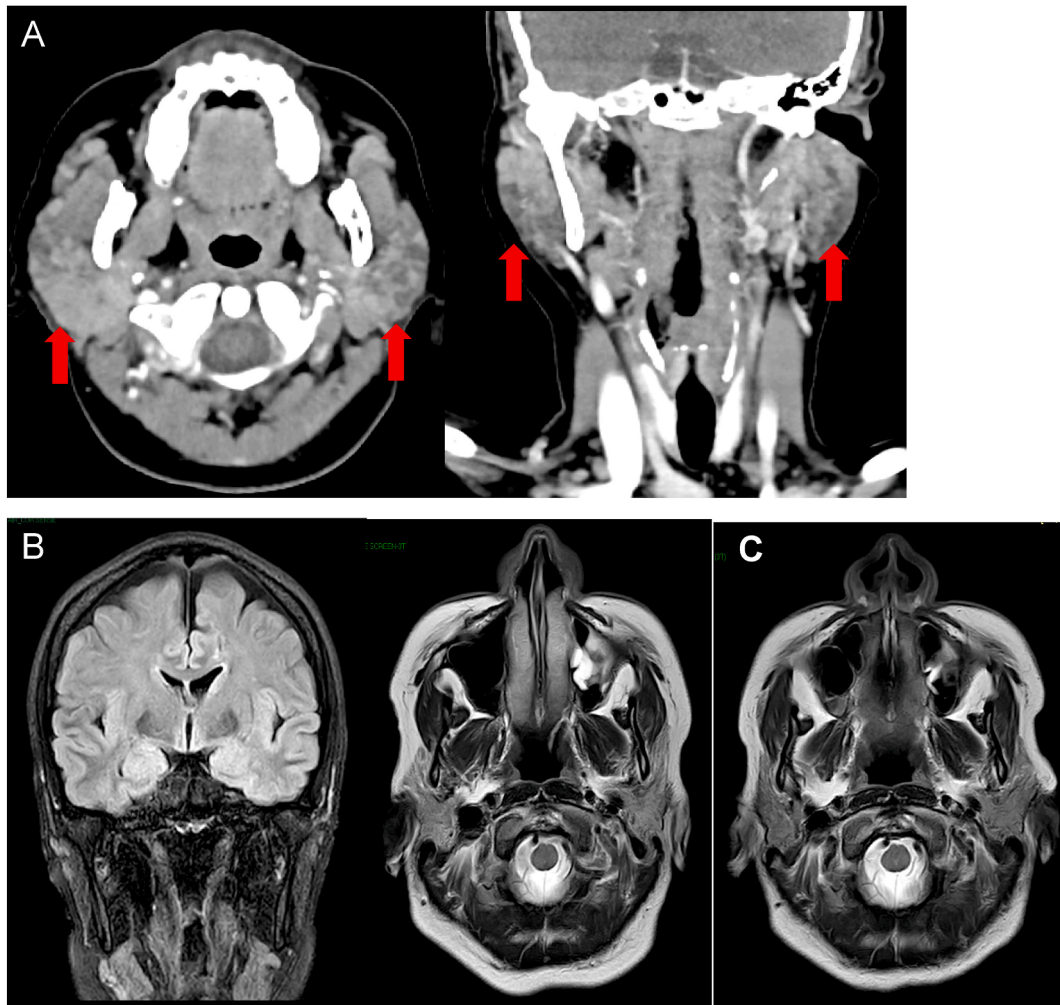


Fig. 5. (A) October 3, 2019 CT Parotid: Bilateral enlarged parotid glands with inhomogeneous nodular enhancement (arrow). There was mild left maxillary sinusitis. (B) March 23, 2019 MR Head: Normal parotids (coronal FLAIR); MR (axial T2). (C) May 6, 2020 MR Head: Normal parotids.

those with uveitis in majority of patients who are black [9]. In contrast, posterior uveitis is more common in the whites, 65%–83% [9]. She had classic sarcoid associated anterior uveitis with keratic precipitates, the large mutton fat type. It responded rapidly to topical and systemic steroid.

Parotid enlargement occurs in about 5–10% of the cases [10], and is usually bilateral. The gland is usually not tender, but firm and smooth. The involvement of her parotids was interesting as well. Right parotid was enlarged during the first episode, bilateral during the second episode and left during the third episode. PET scan in February 2020, at the seventh month of her illness showed FDG uptake in both parotids but she had no complaint. The parotid glands were not clinically and radiologically enlarged at the fourth episode of Heerfordt-Waldenström Syndrome.

We do not know how long the mediastinal and hilar lymphadenopathy have existed. They were first detected at the seventh month of her illness, when the chest x-ray was carried out for investigation of her weight loss and fatigue. Chest Xray at eleven month of treatment showed further decrease in size of lymph nodes at the aortopulmonary window. There is no more hilar enlargement. Fatigue is a common symptom in patient with sarcoidosis, occurring in up to 80% of the patients [11]. The level of fatigue appears to be associated with the presence of extrapulmonary sarcoidosis [12].

Approximately 5% of patients with sarcoidosis have neurological involvement. Sarcoidosis affecting the nervous system is known as neurosarcoidosis. Cranial nerves are most commonly affected, accounting for 5–30% of neurosarcoidosis, in particular the peripheral facial nerve palsy [13]. Facial palsy and acute meningitis due to sarcoidosis tend to have the most favorable prognosis [13].

Cardiac sarcoidosis can be a benign, incidentally discovered condition or a life-threatening disorder causing sudden death [14]. The frequency of involvement varies and is influenced by race; in Japan, more than 25% whereas in US and Europe, only 5% of cases present with cardiac involvement [15]. The presentation can range from asymptomatic conduction abnormalities to fatal ventricular arrhythmia [16,17]. Our patient did not have any cardiac symptoms. The electrocardiogram showed a right bundle branch block but arrhythmia was not observed in the telemetry. The PET scan did not suggest any cardiac inflammation.

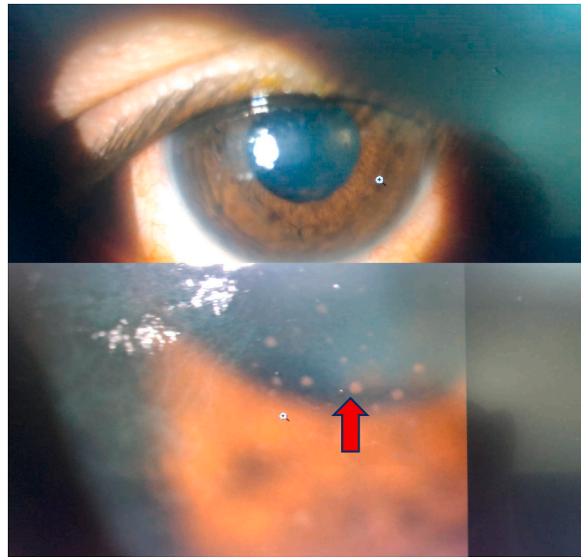


Fig. 6. Bilateral anterior uveitis with keratic precipitates on endothelial surface of cornea, “mutton fat type” (arrow).

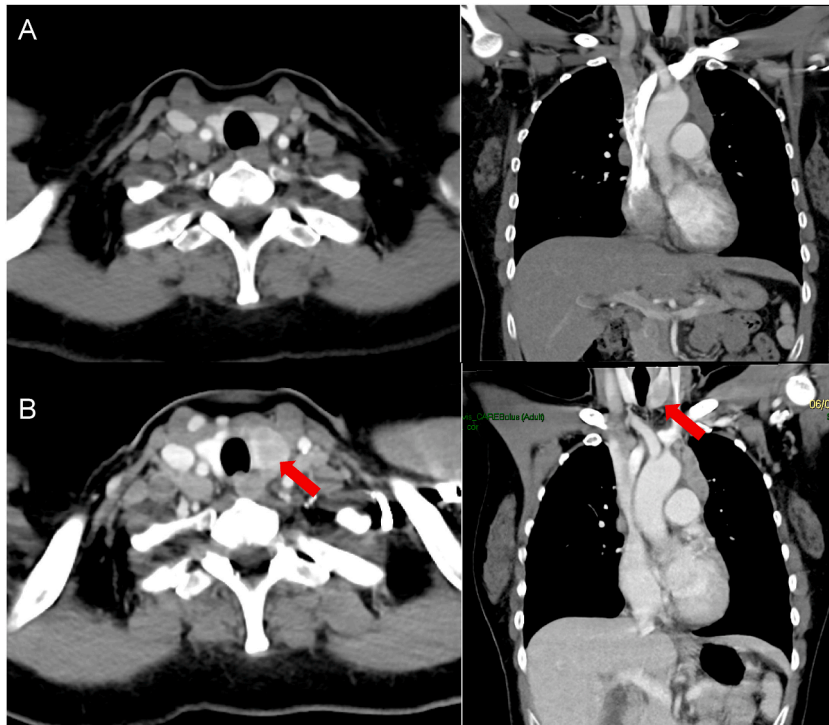


Fig. 7. (A) 3/2/20 CT Thorax: Normal thyroid, axial and coronal images. (B) 6/5/20 CT Thorax: New left thyroid lobe hypodense nodule (arrow), axial and coronal images.

Sarcoidosis can cause diffuse goiter or rarely solitary thyroid nodule [18,19]. Almost all cases are euthyroid, although cases of clinical hypothyroidism caused by diffuse replacement of thyroid have been reported [20,21]. Sarcoidosis with granuloma of thyroid has been found in 4.5% outside Japan [22] and 4% of the autopsy cases in Japan [23]. It can be observed in less than 10% of all sarcoidosis cases and less than 5% of those with cold nodule have non caseating granuloma [24]. Sarcoidosis has been shown to be associated with other autoimmune disorders, especially autoimmune thyroid disease, although being rare. The first case of thyroid involvement was reported in 1938 and with response of thyrotoxicosis upon initiation of steroids [25]. Our patient's last scan at the tenth month of illness showed nodules in her left thyroid. Histology showed the typical granulomatous inflammation. Similar histology is seen in the right supraclavicular lymph node. Fungus and tuberculosis were excluded. Her thyroid function was normal and thyroid antibodies were negative. The nodule resolved with steroid treatment.

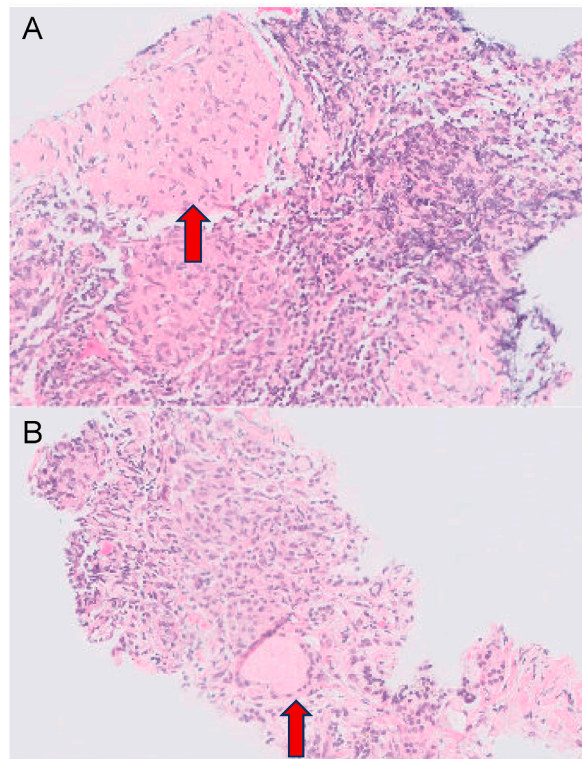


Fig. 8. (A) High Power magnification of right supraclavicular lymph node showing non caseating granulomatous inflammation (Arrowed). (B) High power magnification of thyroid nodule showing ill-defined granulomas.

Serum angiotensin converting enzyme (ACE) levels are raised in 50–80% of patients with active sarcoidosis [26,27] and may be useful in monitoring response to treatment as it reflects the disease activity. It is produced by the granulomas. However, for diagnostic purposes, it is not specific enough [28]. In our case, the level was normal and hence was not useful for monitoring the disease activity.

The natural history, and prognosis of sarcoidosis are highly variable, with a tendency to wax and wane, either spontaneously, or in response to therapy [29]. Spontaneous remissions occur in nearly two-thirds of patients, but the course is chronic or progressive in 10–30% [30]. Fatalities occur in 1–5% of patients, typically owing to progressive respiratory insufficiency or central nervous system or myocardial involvement. The symptoms and/or findings that necessitate corticosteroid therapy remain controversial. In patients with mild disease, such as skin lesions or anterior uveitis, topical steroid therapy may be all that is necessary. In patients with systemic and symptomatic disease, oral corticosteroids are often given. Systemic therapy is clearly indicated for cardiac disease, neurologic disease, eye disease not responding to topical therapy, and hypercalcemia. The use of systemic therapy in pulmonary and other, extrapulmonary disease is less clear cut, but most physicians feel that progressive symptomatic disease should be treated. A patient with persistent pulmonary infiltrates or progressive loss of lung functions and no symptoms may still require therapy. In patients requiring persistent corticosteroid therapy, antimalarial agents and cytotoxic agents should be considered. Systemic steroid was started for our patient as her symptoms were recurrent and associated with neurosarcoidosis and uveitis.

The treatment for tuberculosis in our patient was completed in view of the positive acid bacilli stain seen in the right paratracheal lymph node. Serial chest x-rays showed significant reduction in size of the mediastinal and hilar lymph nodes two months post treatment. It has been suggested that sarcoidosis is due to an immunological response to an infective trigger (for example mycobacteria and propionibacteria) in a genetically predisposed individual [9]. In our patient, mycobacterial DNA was not identified. Conflicting results have been obtained from the studies assessing the etiological role of mycobacterial infection in the pathogenesis of sarcoidosis [9]. Ever since sarcoidosis was first described, its relationship with tuberculosis has been debated. One recent and interesting study in Taiwan [31] showed that patients with TB showed an 8.09-fold higher risk of developing sarcoidosis than non-TB subjects (95% CI = 3.66–17.90), whereas patients with sarcoidosis showed a 1.85-fold higher risk of developing TB than non-sarcoidosis subjects (95% CI = 1.36–2.50). The TB subtype analysis revealed the highest risk of developing sarcoidosis in patients with extrapulmonary TB, and the highest risk of developing extrapulmonary TB was observed in patients with sarcoidosis compared with non-sarcoidosis subjects. Patients with TB showed a higher risk of developing sarcoidosis throughout the follow-up period, but patients with sarcoidosis only showed a higher risk of developing TB within the first year. They proposed that the effects of TB on the development of sarcoidosis involved chronic inflammation and autoimmunity. The study also highlights the difficulty of differentiating sarcoidosis and extrapulmonary TB.

Table 1
Blood investigations.

Investigations	Results
Full blood count	Normal
Renal function	Normal
Glucose	Normal
Liver function	Normal
ESR	18 mm/hour (1–25)
CRP	13.7 mg/L (0.3–5.0)
LDL	5.01 mmol/L (2.6–3.3)
Calcium	2.18 mmol/L (2.15–2.50)
LDH	431 U/L (240–480)
Beta 2 microglobulin	3285 µg/L (0–1900)
Thyroid function	Normal
Anti TPO	Negative
Anti-thyroglobulin	Negative
Thyroid receptor antibody	Negative
Anti-ENA profile	Negative
RA factor	Negative
Anti-DNA ds (October 2019)	< 3 IU/ml
Anti-DNA ds (May 2020)	114 IU/ml (negative < 100)
ANA (October 2019)	1/80, nucleolar
ANA (May 2020)	1/320 homogenous
Anti-cardiolipin IgG and IgM	Negative
Lupus anti-coagulant	Negative
Anti-Ro (SSA)	Negative
Anti-La (SSB)	Negative
ANCA	Negative
C3	1.2 g/L (0.9–1.8)
C4	0.290 g/L (0.1–0.4)
Myeloma screening	Negative
Anti-HIV	Non-reactive
QuantiFERON TB Gold Plus	Negative
Serum Angiotensin Converting Enzyme (ACE)	61 U/L (16–85)

4. Conclusion

Hereto, we report a rare manifestation of sarcoidosis with features of Heerfordt-Waldenström Syndrome along with thyroid and meningeal involvement in a 47-year-old Chinese woman. This may be the first description of sarcoidosis presenting with such extrapulmonary manifestations in the Chinese population. Although Heerfordt-Waldenström Syndrome is a well-recognized entity of sarcoidosis, the awareness of this entity needs to be raised among the clinicians.

We would also like to highlight some salient learning points from this case:

- History taking is important.
- Doctor hopping is not good as the recurrent alternating facial palsy and parotid enlargement was missed.
- Sarcoidosis is a multisystem granulomatous disorder which should be considered as a differential diagnosis even though it is not common in Asia.
- Extrapulmonary tuberculosis and sarcoidosis relationship may be closer than what we know so far.

Consent to publish

Written informed consent was obtained from the patient for publication of this Case Report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Declaration of competing interest

This manuscript has not been published and there is no conflict of interest.

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