Respiratory Medicine Case Reports 51 (2024) 102088

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr

Case Report

Reversed halo sign as a radiological feature of tuberculosis – Report of two cases

Stav Rakedzon [a, b, *], Elad Mor [a, b], Yaniv Dotan [a, b], Ludmila Guralnik [c], Anna Solomonov [a], Einat Fireman Klein [d], Mordechai Reuven Kramer [e, f]

[a] Pulmonary Institute, Rambam Health Care Campus, Haifa, Israel
[b] Ruth and Bruce Rappaport Faculty of Medicine, The Technion–Israel Institute of Technology, Haifa, Israel
[c] Department of Imaging, Rambam Healthcare Campus, Haifa, Israel
[d] Pulmonary Division, Lady Davis Carmel Medical Center, Faculty of Medicine Technion Institute of Technology, Haifa, Israel
[e] Pulmonary Division, Rabin Medical Center, Petah Tikva, Israel
[f] Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

ARTICLE INFO

Keywords:
Reversed halo sign
Tuberculosis
Silica
Silicosis
Ground-glass opacity

ABSTRACT

Reversed halo sign (RHS) is a radiological feature described as a focal, rounded area of ground-glass opacity surrounded by a ring of consolidation. In this report we describe two unique radiological cases demonstrating diffuse bilateral infiltrates with multiple RHSs in chest CT scans. Both patients were ultimately diagnosed as having tuberculosis (TB) and had been exposed to silica in the past. This report presents for the first time an association between silica exposure and RHS on CT scans among TB patients. It highlights the importance of having a high index of suspicion for TB in similar scenarios.

Abbreviations

Al	Aluminum
BAL-	Bronchoalveolar lavage
C	Carbon
CT	Computed tomography
CVA	Cerebrovascular accident
GGO	Ground-glass opacity
K	Potassium
NSCLC	Non-Small Cell Lung Cancer
O	Oxygen
RHS	Reversed halo sign
RUL-	Right upper lobe
S	Sulfur
SEM	Scanning Electron Microscopy
Si	Silicon

* Corresponding author. Pulmonary Institute, Rambam Health Care Campus, Haifa, Israel.
E-mail address: s_rakedzon@rambam.health.gov.il (S. Rakedzon).

https://doi.org/10.1016/j.rmcr.2024.102088
Received 21 May 2024; Received in revised form 4 June 2024; Accepted 9 July 2024
Available online 10 July 2024

TB	Tuberculosis
TBB	Trans bronchial lung biopsy

1. Introduction

Reversed halo sign (RHS) is a radiological feature on computed tomography (CT) scans, described as a focal, rounded area of ground-glass opacity (GGO) surrounded by a more or less complete ring of consolidation [1]. This sign has a broad differential diagnosis including various infections and noninfectious etiologies, with the most frequent etiology being an organizing pneumonia.

Here we describe two patients presented with different clinical symptoms who subsequently were diagnosed with tuberculosis (TB). Both had no significant findings on physical examination or laboratory tests, however, their CT scans demonstrated diffuse bilateral infiltrates with multiple RHSs.

2. Cases presentation

2.1. Patient number 1

A 65-year-old male presented to the emergency department with complaints of severe weakness resulting in recurrent falls and weight loss of 8 kg for the past 6 months. In addition, he complained of chronic purulent cough for the past two years. Dyspnea, fever and night sweats were ruled out by the patient.

The patient's medical history included hypertension and a single episode of cerebrovascular accident (CVA). He was a heavy smoker (100 pack years), worked as a tile installer and had been exposed to silica. Additionally, domestic exposure to birds was documented.

Three years prior to his admission, he was diagnosed with early stage non-small cell lung cancer (NSCLC) and underwent right upper lobe (RUL) apical segment resection, without neoadjuvant or adjuvant therapy.

Upon his admission, the patient was severely cachectic. His vital signs were within normal limits with oxygen saturation (SpO2) 94 % on room air. No pathological findings were documented on physical examination.

Laboratory tests demonstrated mild normocytic anemia (Hb 12.5 mg/dl) and mild thrombocytosis (396K). Leukocyte count, arterial blood gas, liver and kidney function tests were within normal limits.

Chest X-ray revealed patchy infiltrates located at the upper and middle lobes with sparing of the lower lobes. CT scan demonstrated interstitial infiltrates with GGO in both lungs with relative sparing of subpleural regions and lower lobes. Additionally, multiple small RHS were observed in the same areas (Fig. 1a–c). A small cavitation of 1.4 cm was identified in the RUL.

Of note, the patient performed annual CT scans starting 5 years prior to the patient admission due to his smoking and cancer history. A revision of these previous CT scans demonstrated focal infiltrates with cluster sign pattern located at the left upper lobe undergoing a gradual expansion over the years until most of the lung parenchyma was bilaterally involved. No RHS was documented in these past CT scans.

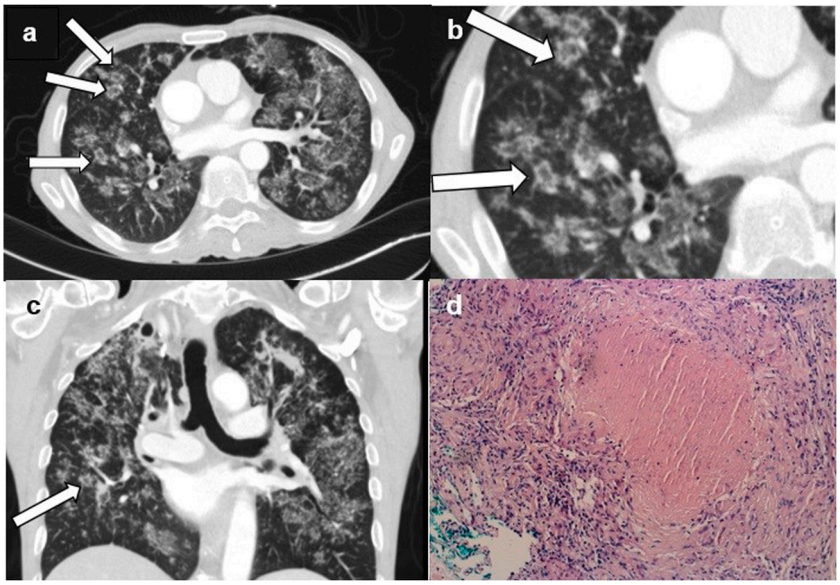

Fig. 1. Radiological and histopathological findings of patient number 1. Axial (a,b) and coronal (c) chest CT planes show rounded areas of ground-glass opacities surrounded by a complete ring of consolidation (reversed halo signs, arrows). No lymphadenopathy is seen. (d) An H&E stained section of trans bronchial lung biopsy taken from the right upper lobe of patient number 1-showing a chronic inflammation composed of lymphocytes and macrophages forming necrotizing and non-necrotizing granulomas are seen, compatible with the diagnosis of TB.

Trans bronchial lung biopsy (TBB) and bronchoalveolar lavage (BAL) were performed from the posterior segment of the RUL. PCR and microbiology cultures were positive for *Mycobacterium tuberculosis*. Biopsy demonstrated chronic inflammation with necrotizing and non-necrotizing granulomas (Fig. 1d). Ziehl-Neelsen staining for Mycobacteria was positive. Upon diagnosis, anti tuberculosis was rapidly initiated. During his hospitalization, the patient rapidly deteriorated due to septic shock. Eventually the patient succumbed to his disease 5 days following the diagnosis.

2.2. Patient number 2

A 58-year-old male referred to the pulmonary clinic, complaining of chronic purulent cough and exertional dyspnea for the last few months. The patient was a heavy smoker (57 pack years) and as a construction worker, he was exposed to silica through sandblasting and artificial stone cutting.

Physical examination and laboratory investigations were within normal limits. CT scan demonstrated bilateral RHS at the upper lobes and the upper segments of the lower lobes. The basal segments of the lower lobes and the subpleural areas were spared. No significant lymphadenopathy was documented (Fig. 2a and b). Cryo trans bronchial lung biopsy (Cryo TBB) was performed from the anterior segment of the RUL. Biopsy demonstrated fragments of bronchial and alveolar parenchyma with no granulomas. Ziehl-Neelsen staining was negative. However, PCR for *Mycobacterium tuberculosis complex* was positive. Treatment for tuberculosis was initiated. As part of occupational workup, the sample was also analyzed by Scanning Electron Microscopy (SEM) that revealed silica rich particles, some of which were mixed with Aluminum and Titanium. (Fig. 3).

A following CT conducted five months following the first CT scan and two months following treatment starting point demonstrated multiple cavitations and consolidations. Additional micronodules were identified in both upper lobes. An additional CT scan performed two months later demonstrated a mild radiological improvement evident by a reduction in micronodule numbers and cavitations' shrinkage (Fig. 2c and d). The patient was followed for nine months and was clinically improved.

3. Discussion

TB is an infectious disease caused by *Mycobacterium tuberculosis* and is a leading cause of death worldwide, according to the World Health Organization (WHO) [2].

In 2022, 7.5 million people were diagnosed with new episodes of TB (defined as both new and relapse cases) worldwide. Of these, 83 % had pulmonary TB and 17 % had extrapulmonary TB. Radiological imaging is a key modality during the diagnosis of pulmonary TB. Active pulmonary TB is usually characterized by either heterogeneous consolidations, cavitations or bronchogenic spread known as a "tree-in-bud" pattern on CT scans [3]. Other radiological features of TB are less common and are associated with other pulmonary diseases. One of these features is the RHS. RHS has been previously described in infectious diseases, malignancies and inflammatory diseases. The differential diagnoses of RHS are summarized in Table 1 [4–6].

Several case reports and small retrospective studies have reported RHS in CT scans of TB patients [7,8]. Patients clinical and radiological characteristic that were available are summarized in Table 2.

The incidence of RHS among active pulmonary TB patients was as high as 17 % in one case series [7]. RHS in pulmonary TB is characterized by a nodular pattern, composed of small nodules located within the surrounding ring and inside the reversed halo, most

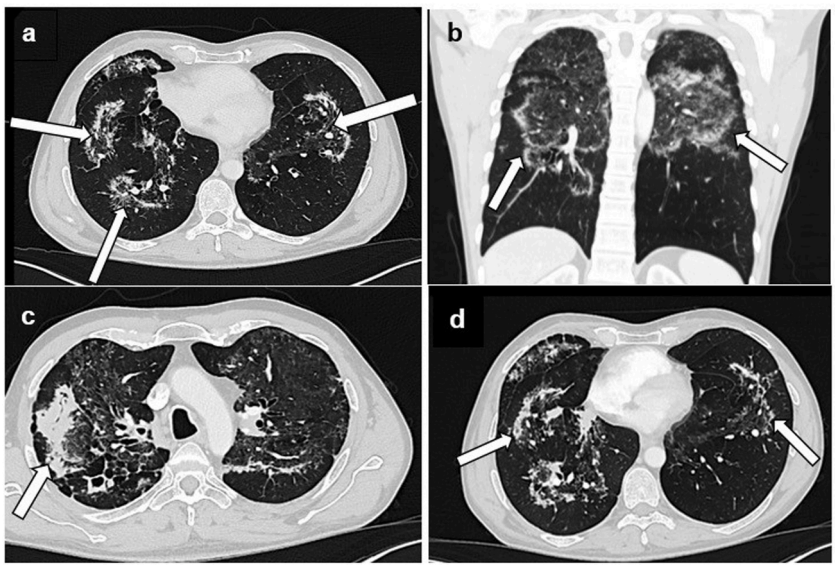

Fig. 2. Chest CT scans of patient number 2. Axial (a) and coronal (b) planes show rounded areas of ground-glass opacities surrounded by a complete ring of consolidation (reversed halo signs, arrows) in the upper lobes. No lymphadenopathy is seen.
A follow up HRCT scan, two months following the treatment starting point. Multiple cavitations, cluster signs (c) and RHS (d) are present in both upper lobes, however more prominent on the right.

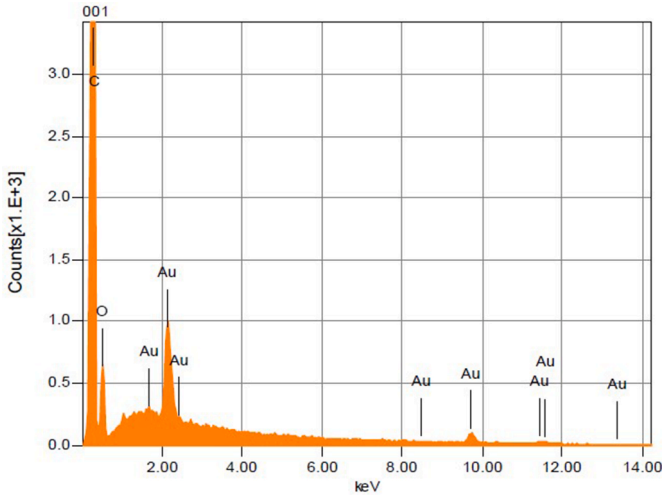

Fig. 3. Mineral analysis of one of the particles identified in the lung biopsy using the SEM (Scanning Electron microscope) JCM-6000PLUS. Particles content was determined using an energy-based spectrometer and a petrographic microscope to identify minerals. This particle contains silicon (Si), Sulfur (S), Aluminum (Al), carbon (C), oxygen (O), and potassium (K). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 1
The differential diagnoses of Reversed halo sign.

Fungal infections	
	Mucormycosis
	Invasive aspergillosis
	Paracoccidioidomycosis
	Histoplasmosis
	Cryptococcosis
	Pneumocystis pneumonia
Bacterial infections	
	Slow-resolving pneumonococcal pneumonia
	Chlamydia psittaci
	Legionella pneumophila
Viral infections	
	Coronavirus in the context of COVID-19
Mycobacterial infections	
	Mycobacterium tuberculosis
Systemic diseases	
	Granulomatosis with polyangiitis
	Sarcoidosis
	Eosinophilic granulomatosis with polyangiitis
	Dermatomyositis
Neoplastic diseases	
	Lymphomatoid granulomatosis
	Non-small cell lung cancer
Various pulmonary diseases	
	Cryptogenic organizing pneumoniab
	Acute fibrinous and organizing pneumonia
Iatrogenic	
	Radiofrequency/microwave ablation of pulmonary malignancies
	Radiation pneumonitis
Miscellaneous	
	Lipoid pneumonia
	Pulmonary thromboembolism

probably representing small clusters of granulomas. Interestingly, the micronodular pattern of RHS was not observed in cases of organizing pneumonia [8]. The differential diagnosis for nodular RHS include various granulomatous diseases such as sarcoidosis or lymphomatoid granulomatosis that were ruled out in our cases [9,10].

Compared to previous reports, in which most patients had a solitary RHS or a small amount of RHS foci [8], in our cases multiple RHS were observed. Furthermore, additional radiological signs supporting the diagnosis of TB (such as consolidations, cavitations or lymphadenopathy) were absent [3]. These unusual radiological characteristics shed light on the wide spectrum of TB radiological patterns. Although it made the diagnosis of TB challenging in our cases, it stresses the importance of considering the diagnosis of TB in similar scenarios with RHS on imaging.

Table 2
TB Patients' with RHS clinical and radiological characteristic.

	Cases	Age	Gender	Number of RHS	Nodular RHS	Other CT findings	Documented exposure	Smoking history
Patient number 1	1	65	M	>5	Yes	- clusters of small nodules - GGO - small cavitation	Silica	Smoker
Patient number 2	2	58	M	>5	Yes	- small nodules	Silica	Smoker
Marchiori et al. [13]	3	32	F	>5	Yes	- consolidations - cavitations - small nodules - bronchial wall - thickening	None	Smoker
Martini et al. [7]	4	36	M	1	Yes	- N/A	N/A	Smoker
Martini et al. [7]	5	26	M	5	Yes	- N/A	N/A	Never smoker
Martini et al. [7]	6	80	M	1	Yes	- N/A	N/A	Never smoker
Martini et al. [7]	7	30	M	4	Yes	- N/A	N/A	Never smoker
Martini et al. [7]	8	30	M	2	Yes	- N/A	N/A	Smoker

M- Male, F- Female, RHS- Reversed Halo Sign, GGO- Ground glass opacities.

Interestingly, both patients presented in the current report were previously exposed to silica. However, the radiological spreading patterns of the nodules were not typical for silicosis and no significant lymphadenopathy was observed. In terms of pathological findings, no silicotic nodules were identified, and no silica crystals were detected under polarized light. Interestingly, however, SEM test revealed silica rich particles in the biopsy material from the second patient. It is possible that the exposure to silica even without overt silicosis (in the absence of radiological or pathological findings), may increase the susceptibility to TB infection, as previously reported [11,12]. However, future studies are needed to further support these findings and provide a rational biological explanation for this phenomenon.

4. Conclusion

In this report we describe two unique cases with silica exposure and unusual clinical and radiological characteristics that were ultimately diagnosed as TB. Both shared similar radiological patterns of RHS which are not typical for TB. while lacking common CT signs supporting the diagnosis of TB, these unique cases emphasize the wide spectrum of radiological findings in TB and demonstrate the importance of having a high index of suspicion for TB in similar clinical and radiological scenarios, especially in countries with a low burden of tuberculosis.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Stav Rakedzon: Writing – original draft, Investigation, Data curation. **Elad Mor:** Writing – review & editing, Methodology. **Yaniv Dotan:** Writing – review & editing, Validation. **Ludmila Guralnik:** Formal analysis. **Anna Solomonov:** Supervision, Investigation. **Einat Fireman Klein:** Writing – original draft. **Mordechai Reuven Kramer:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

None.

References

[1] D.M. Hansell, A.A. Bankier, H. MacMahon, T.C. McLoud, N.L. Müller, J. Remy, Fleischner Society: glossary of terms for thoracic imaging *Radiology* 246 (3) (2008) 697–722, https://doi.org/10.1148/radiol.2462070712.
[2] S. Bagcchi, WHO's global tuberculosis report 2022, Lancet Microb. 4 (1) (2023) e20, https://doi.org/10.1016/S2666-5247(22)00359-7.
[3] M.T.A. Wetscherek, T.J. Sadler, J.Y.J. Lee, S. Karia, J.L. Babar, Active pulmonary tuberculosis: something old, something new, something borrowed, something blue, Insights Imag. 13 (1) (2022) 3, https://doi.org/10.1186/s13244-021-01138-8.
[4] V.N. Maturu, R. Agarwal, Reversed halo sign: a systematic review, Respir. Care 59 (9) (2014) 1440–1449, https://doi.org/10.4187/respcare.03020.
[5] S.P. Georgiadou, N.V. Sipsas, E.M. Marom, D.P. Kontoyiannis, The diagnostic value of halo and reversed halo signs for invasive mold infections in compromised hosts, Clin. Infect. Dis. 52 (9) (2011) 1144–1155, https://doi.org/10.1093/cid/cir122.
[6] M.C.B. Godoy, C. Viswanathan, E. Marchiori, et al., The reversed halo sign: update and differential diagnosis, Br. J. Radiol. 85 (1017) (2012) 1226–1235, https://doi.org/10.1259/bjr/54532316.
[7] K. Martini, A. Loubet, A. Bankier, et al., Nodular reverse halo sign in active pulmonary tuberculosis: a rare CT feature? Diagn. Interv. Imag. 101 (5) (2020) 281–287, https://doi.org/10.1016/j.diii.2020.01.013.
[8] E. Marchiori, G. Zanetti, K.L. Irion, et al., Reversed halo sign in active pulmonary tuberculosis: criteria for differentiation from cryptogenic organizing pneumonia, AJR Am. J. Roentgenol. 197 (6) (2011) 1324–1327, https://doi.org/10.2214/AJR.11.6543.
[9] R.E. Benamore, G.L. Weisbrod, D.M. Hwang, et al., Reversed halo sign in lymphomatoid granulomatosis, Br. J. Radiol. 80 (956) (2007) e162–e166, https://doi.org/10.1259/bjr/46361210.

[10] B. Pattnaik, P.B. Sryma, S. Mittal, K. Madan, Reversed halo sign: uncommon presentation of a common disease, Lung India 37 (2) (2020) 182–183, https://doi.org/10.4103/lungindia.lungindia_360_19.
[11] R. Ehrlich, P. Akugizibwe, N. Siegfried, D. Rees, The association between silica exposure, silicosis and tuberculosis: a systematic review and meta-analysis, BMC Publ. Health 21 (1) (2021) 953, https://doi.org/10.1186/s12889-021-10711-1.
[12] R.L. Cowie, The epidemiology of tuberculosis in gold miners with silicosis, Am. J. Respir. Crit. Care Med. 150 (5 Pt 1) (1994) 1460–1462, https://doi.org/10.1164/ajrccm.150.5.7952577.
[13] E. Marchiori, R.D. Grando, C.E. Simões Dos Santos, et al., Pulmonary tuberculosis associated with the reversed halo sign on high-resolution CT, Br. J. Radiol. 83 (987) (2010) e58–e60, https://doi.org/10.1259/bjr/22699201.