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Chylothorax associated with sarcoidosis: a review of the literature

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Abstract. *Objective:* To review the medical literature regarding chylothorax associated with sarcoidosis. *Methods:* A literature review of all reported cases of sarcoidosis-associated chylothorax, we included a novel case report to the analysis. *Results:* Of sixteen cases included in the study, 10 were women (62.5%), mean age 47±17years. In 6 subjects (37.5%) chylothorax was part of the initial presentation of sarcoidosis. Four subjects (25%) additionally suffered from lymphedema and chylous ascites, and one from chylous ascites only. Thoracic lymphadenopathy was reported for 13/16 subjects (81.3%) and lung parenchymal disease in 8/16 (50%). Compression of the thoracic duct was considered as a causative factor in 10 cases (62.5%). One case was attributed to granulomatous pleural inflammation, one to generalized lymphangiectasia, and no specific causative factors were identified in 4 remaining cases (25%). Overall mortality rate was 18.8% (3/16 subjects). Of note, all the subjects treated with corticosteroids survived. *Conclusions:* Since the association of sarcoidosis with chylothorax is exceedingly rare, alternative etiologies should be pursued even when chylothorax develops in a subject with preexisting sarcoidosis. However, the possibility of sarcoidosis should be entertained when other etiologies for a newly diagnosed chylothorax are ruled out. A multidisciplinary approach is required for optimal management, both for elucidating the diagnosis and for employing therapy, which could be multimodal. A trial of immunosuppressive therapy with corticosteroids should be considered.

Key words: Sarcoid, Chylothorax, Pleural effusion, Lymphedema, Chylous ascites

Introduction

Sarcoidosis is a systemic disease most commonly affecting the lungs and thoracic lymph nodes (1). Pleural effusions are uncommon in subjects with sarcoidosis and may result from other causes (2). In particular, chylothorax is an exceedingly rare manifestation of sarcoidosis. We have recently treated a subject with progressive lymphedema and bilateral chylothorax who was ultimately diagnosed with sarcoidosis, and who required multimodal therapy. This has prompted us to perform a literature review of sarcoidosis-related chylothorax which is hereby reported.

Methods

This is a literature review of reported cases of sarcoidosis-associated chylothoraxes. While it cannot be considered a formal systematic review, since it includes only case reports, the review was nevertheless conducted in accordance with the PRISMA 2020 statement. We conducted searches of the PubMed/MEDLINE and EBSCO bibliographic databases up to April 15th 2021. The search was done using the keywords "sarcoid" or "sarcoidosis" combined with "chylothorax", "chylous", or "chyle". In addition, a search using MESH terms " sarcoidosis" or "sarcoid" and "chylothorax" or "chyle" or "chylous"

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was performed. Abstracts of all identified article were independently reviewed by two investigators (O.W. and L.I.S.). If an abstract was considered potentially relevant by either investigator, the full-text article was reviewed and assessed for inclusion and exclusion criteria. The reference lists of each publication were further reviewed for additional cases. We included all articles reporting cases of chylothoraxes associated with sarcoidosis, in which both the diagnosis of chylothorax (pleural fluid with triglyceride≥110mg/dL or the presence of chylomicrons) as well as the diagnosis of sarcoidosis (supported by histological evidence of granulomas) could be ascertained. We excluded cases in which other etiologies for granulomatous inflammation were present, or in which chylothorax was deemed to result from causes other than sarcoidosis (such as trauma or surgery). When articles included duplicate data, we included only one report of the data.

For publications included in the analysis we recorded the total number of subjects with sarcoidosis-associated chylothorax, as well as additional relevant data including the following: subject's age and gender, side of chylothorax, pleural fluid characteristics, presence of concurrent chylous ascites or lymphedema, whether there was lung parenchymal or thoracic lymph nodes involvement with sarcoidosis, treatment, response to therapy and outcome (survival). Success of therapeutic interventions was defined as improvement leading to a situation in which no further pleural fluid draining procedures were required. Publications that included the relevant information were included in this review.

Results

Case report

The 72-years-old female subject was admitted for the evaluation of increasing bilateral leg edema and dyspnea. Previous medical history included well controlled type 2 diabetes mellitus and hypertension; she was a never smoker. Physical examination revealed pitting edema of both legs and left arm, and decreased breath sounds over lower lungs fields bilaterally. Pleural effusions were demonstrated by chest X-ray.

The patients first presented with bilateral pleural effusion and leg edema 15 months previously at another hospital. At that time, the effusions were diagnosed as bilateral chylothorax. Laboratory studies, chest and abdominal CT were unrevealing. Liver sonography which included transient elastography ruled out cirrhosis and portal hypertension. Lower limbs lymphoscintigraphy with ^{99m}Tc-nanocolloid demonstrated significantly delayed lymphatic transport confirming the diagnosis of lymphedema, without localization of an obstruction or extravasation of lymphatic fluid. A thoracoscopic pleural biopsy demonstrated chronic nonspecific inflammation without signs for malignancy or infection and did not promote a specific diagnosis. The subject was treated with subcutaneous octreotide 100μL three times a day, low-fat diet with medium chain triglycerides (MCT) supplementation and bilateral chest tube drainage. Chest drains were ultimately removed despite continuous drainage, and the subject was discharged to ambulatory follow-up. During the ensuing 15 months lymphedema gradually worsened and involved the arms, while thoracentesis was occasionally required, despite adherence to dietary advice.

She was hospitalized in our department, where therapy with dietary modifications was reconstituted and octreotide was renewed. The left sided effusion was tapped, revealing milky fluid, lymphocyte predominant (85%), marginally exudative (pleural fluid and serum protein 2.7 g/L and 5.4 g/L, ratio 0.5, pleural fluid and serum lactate dehydrogenase 78 IU/L and 160 IU/L respectively, ratio 0.49), and elevated triglyceride level of 164mg/dL fulfilling criteria for chylothorax. Microbiological studies were negative for infection, and no malignant cells were noted on cytology. She underwent left thoracoscopy, during which lung biopsies and talc pleurodesis were performed. Noncaseating granulomas were demonstrated on lung biopsy specimens, suggesting the diagnosis of sarcoidosis. There was no significant FDG accumulation on ^{18}F-FDG PET-CT imaging, yet total body CT disclosed post-procedural changes in the left pleural space, right pleural effusion, and mild ascites, without evidence for parenchymal lung disease, malignancy, or lymphadenopathy (Figure 1A-B). While the pleurodesis procedure was successful, the subject remained extremely symptomatic and debilitated from massive lower limbs edema and right chylothorax. Therapy with oral prednisone 30mg/day (0.5mg/kg) was initiated and she was scheduled for a right pleuroscopy with attempted talcage 6 week later. During

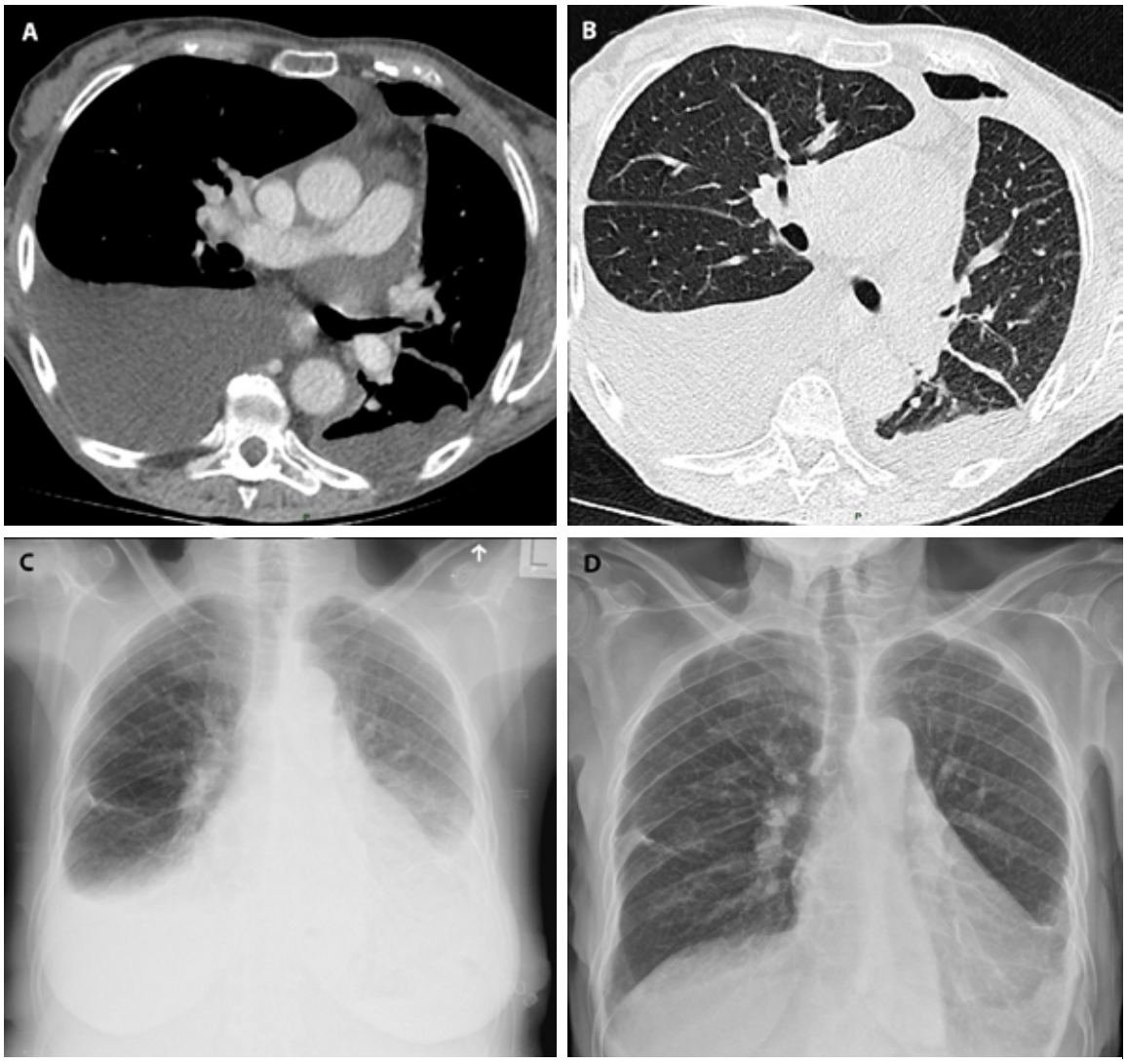

Figure 1. Chest imaging of the subject (no. 1)
(A) and (B) chest CT images of the subject on mediastinal window (A) and lung window (B), demonstrating post-operative changes in the left pleural space and moderate right pleural effusion. There is no evidence of parenchymal or lymph nodes involvement by sarcoidosis. (C) Chest X-ray performed 2-weeks after left thoracoscopic talc pleurodesis. The right pleural effusion has completely resolved after 5 months of medical therapy (D).

that scheduled follow-up, the subject reported significant improvement of dyspnea, resolution of edema at the arms, and decreased legs' edema, allowing her to ambulate freely. Sonography demonstrated almost complete resolution of right and left effusions, and gradual tapering of prednisone was commenced. Five months following initiation of corticosteroid therapy she is continuing to improve clinically and radiographically; prednisone is currently at 10mg/day with continued dose reduction (Figure 1C-D).

Literature review

Our literature search yielded 128 articles, of which 12 met the inclusion and exclusion criteria, additional 3 relevant reports were identified from references lists. Each publication reported one case of sarcoidosis-associated chylothorax, totaling 16 cases including the subject hereby reported (Figure 2) (3-17).

Ten of 16 cases were women (62.5%), with mean age at presentation of chylothorax being 47 ±17years.

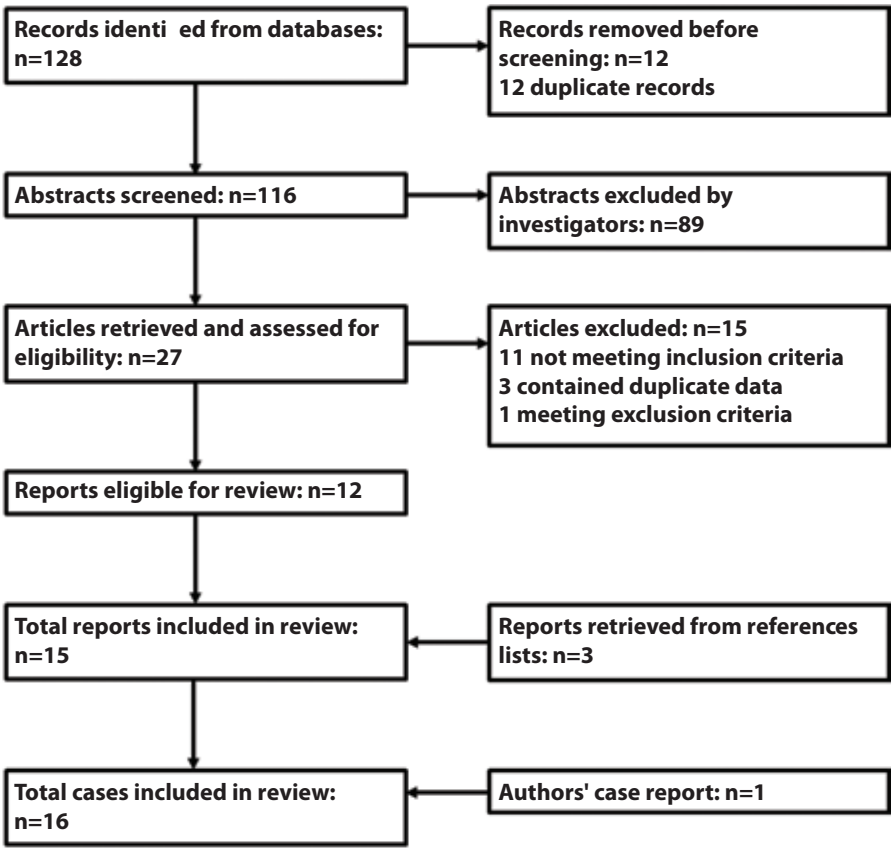

Figure 2. Flow-chart of the literature review and articles inclusion and exclusion process.

Details of the cases are summarized in Table 1. In 6 subjects (37.5%) chylothorax was part of the initial presentation of sarcoidosis, and in those cases the time to diagnosis ranged from 1-16 months. The effusions were right sided in 9 subjects, left sided in 3, and bilateral in 4 (corresponding to 56.3%, 18.7%, and 25% respectively). All effusions were lymphocytic predominant. Triglyceride concentrations ranged from 97 to 2513mg/dL and were lower than 110mg/dL in only one case. In that case, the diagnosis of chylothorax was ascertained by the presence of chylomicrons by lipoprotein electrophoresis of the pleural fluid. Effusions' glucose was 80mg/dL or higher in all cases and pH was at least 7.4. The effusions were classified as exudates in 7 cases, as a transudate in 1 case, and could not be classified due to lack of reporting in 8 cases.

Four subjects (25%) additionally suffered from lymphedema and chylous ascites, and one from chylous ascites only (6.3%). As to other thoracic involvement by sarcoidosis, lymphadenopathy was reported for 13/16 subjects (81.3%) and lung parenchymal disease in 8/16 (50%).

Regarding possible mechanisms resulting in chylothorax, compression of the thoracic duct by enlarged lymph nodes was considered as the causative factor in 8 cases (50%) and was also noted in another subject who also had severe pleural inflammation. Another subject had significant fibrotic adhesions affecting the thoracic duct. In the remaining 6 cases (37.5%) there were no signs of thoracic duct obstruction. One case of chylothorax was attributed to granulomatous pleural inflammation, one to generalized lymphangiectasia, and no specific causative factors were suggested in 4 remaining cases (25%). There were no differences in presentation or response to treatment between subjects when categorized according to pathophysiologic mechanisms of chylothorax development.

All but one subject, who was diagnosed only postmortem, received therapy directed to treat chylothorax in addition to drainage procedures.

Table 1. Characteristics of cases with sarcoidosis-associated chylothorax.

No	Gender	Age	Presenting symptom?	Side	Effusion type	Other involvement by sarcoidosis				Treatment	Response to medical Tx?	Outcome	Reference
						Ascites	Lymphedema	Lung parenchyma	Thoracic LN				
1	F	70	Yes	Bil	Borderline exudate	1	1	0	0	Steroids, octreotide, diet, pleurodesis	Yes	Survival	Current report
2	F	54	No	Bil	Exudate	1	1	0	1	octreotide, diet	No	Fatal	3
3	F	47	No	Bil	Transudate	1	1	1	0	Diet	Yes	Survival	4
4	F	72	Yes	Lt	Exudate	0	0	0	1	pleurodesis	NR	Survival	5
5	F	22	Yes	Rt	NR	0	0	1	1	Steroids, octreotide, diet	Yes	Survival	6
6	M	45	Yes	Rt	Exudate	0	0	1	1	Steroids, octreotide	Yes	Survival	7
7	M	40	No	Rt	NR	0	0	1	0	Steroids, pleurodesis	No	Survival	8
8	F	34	No	Rt	NR	0	0	1	1	Steroids	Yes	Survival	9
9	F	46	No	Rt	Exudate	0	0	0	1	Steroids, octreotide, diet	Yes	Survival	10
10	M	28	Yes	Rt	NR	0	0	1	1	Steroids, diet	Yes	Survival	11
11	F	51	No	Rt	NR	1	1	1	1	Diet	No	Fatal	12
12	F	33	No	Bil	Exudate	1	0	1	1	Steroids, diet	No	Survival	13
13	F	81	No	Lt	NR	0	0	0	1	None, diagnosed postmortem	NR	Fatal	14
14	M	27	Yes	Lt	NR	0	0	0	1	Steroids	Yes	Survival	15
15	NA	64	No	Rt	Exudate	0	0	0	1	Steroids	No	Survival	16
16	M	45	No	Rt	Exudate	0	0	0	1	Steroids + pleurodesis	Yes	Survival	17

In case no. 3, the authors speculate that the effusion was a transudate because of severe protein-losing enteropathy and hypoalbuminemia.

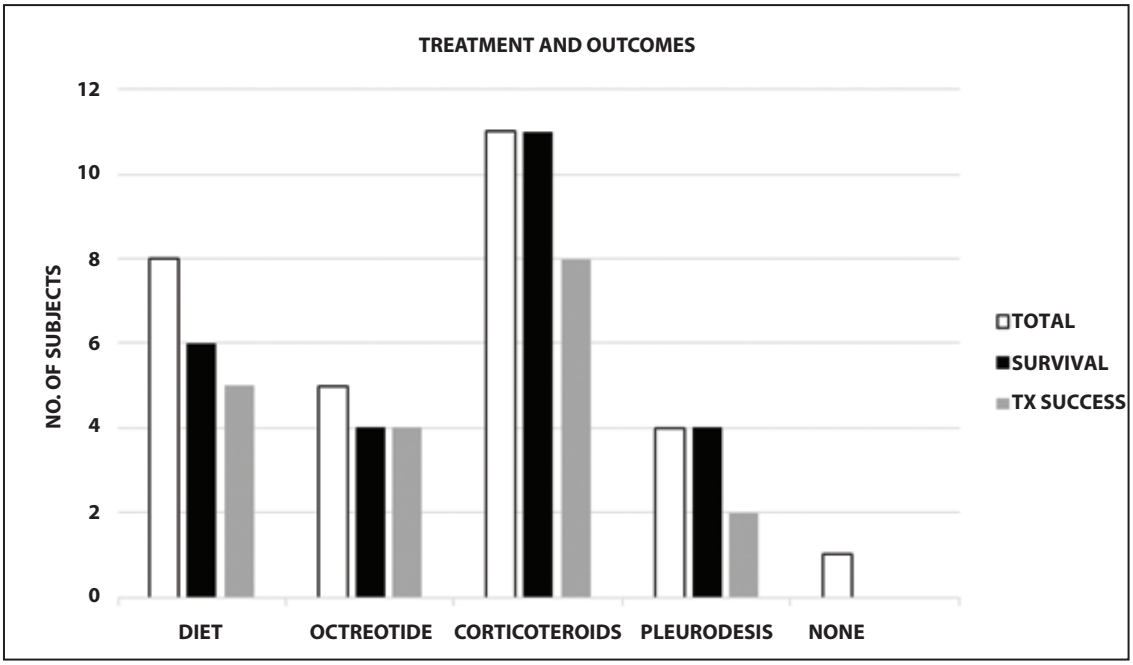

Figure 3. Patients' outcomes according to treatment.
Total number of patients exceeds 16 since some received more than one treatment.

Therapeutic interventions included dietary modifications in 8 subjects (50%), subcutaneous injections of octreotide in 5 (31.3%), corticosteroid therapy in 11 (68.8%), and talc pleurodesis in 4 (25%). Initial corticosteroids doses were in the range of 0.5-1mg/kg prednisone daily in all but one cases. In the remaining case, the initial dose was 20mg/day. No other immunosuppressive therapies were used. Four subjects who were treated with both corticosteroids and octreotide responded well to medical therapy. Response rates to different specific therapies is shown in Figure 3. Mortality rate was 18.8% (3/16 subjects). Of note, all the subjects treated with corticosteroids survived. (Figure 3)

Discussion

Pleural effusion is a well-recognized yet uncommon manifestation of sarcoidosis (18-19). In a large retrospective study which included 195 subjects with sarcoidosis, pleural effusions were reported in 3 subjects only (1.5%) (7). The frequency of pleural effusions on CT scans was reported as 8.1% (5/61) among sarcoidosis patients in another study, yet the causes of effusions were not reported (20). The most accurate estimates of pleural effusion in subjects with sarcoidosis can probably be obtained from the study by *Huggins et al.* which prospectively performed thoracic sonography on 181 consecutive outpatients. With this sensitive technique, pleural effusions were detected in 5 subjects (2.8%) but were attributable to sarcoidosis in only 2 cases (1.1%) (2). Chylothorax is even more unusual and have been described in only a few case reports of sarcoidosis patients.

Chylothorax is usually the result of either disruption of the thoracic duct or obstruction to lymphatic drainage (21). Other mechanisms include lymphatic abnormalities or ectasias from various causes (such as in yellow-nail syndrome) and transdiaphragmatic migration of chylous ascites fluid (21-22). The most common etiologies include traumatic causes (including surgical etiologies) and malignancies. Lymphatic disorders also include lymphangioleiomyomatosis (23-24) and pulmonary lymphangiectasias. Chylous ascites may result from liver cirrhosis and nephrotic syndrome, amongst other causes. Rarely, chylothorax were associated with infection such as tuberculosis or parasitic infestation (22). Occlusion of the thoracic duct by lymphadenopathy may be a relevant mechanism in subjects with sarcoidosis, as suggested in over half of the cases in our literature review. However, in a significant minority of cases, no thoracic duct

abnormalities were detected. In some of these cases, chylothorax was attributed to either pleural inflammation or to lymphangiectasia. In this regard, it is noteworthy that sarcoidosis may promote lymphangiogenesis of "atypical" heterogenous microscopic lymphatic vessels, which tend to concentrate around granulomas (25). In fact, increased lymph vessel counts were shown in endomyocardial biopsy specimens from subjects with cardiac sarcoidosis even in the absence of granulomas (26). A similar process may also occur in other granulomatous diseases such as tuberculosis. It has been suggested that a bidirectional relationship may exist, in which granulomatous inflammation propagates lymphangiogenesis, and in turn, lymphatic vessels promote spread of granulomas (27). Thus, we assume that sarcoidosis may produce generalized lymphatic derangements that could result in lymphatic leakage. These leaks may present in the forms of chylothorax, chylous ascites, lymphedema, or a combination of them.

Management of chylothorax usually begins with conservative therapy, which includes pleural drainage, dietary modifications towards a high-protein, low-fat diet, and somatostatin analogues (22). Such conservative management aimed at reducing chyle production and decreasing lymph flow is not always successful. When conservative, medical therapy fails, several surgical interventions can be employed, either directed at the thoracic duct, or the pleural spaces such as talc pleurodesis (21-22). However, therapy aimed at a specific etiology might sometimes be relevant. In the current review, systemic steroids were employed in most cases and seemed to be associated with favorable outcomes. We believe that a trial of immunosuppression is worthwhile in sarcoidosis-associated chylothorax.

Our study is very limited by the small number of published cases, lack of prospective studies, and possibility of publication bias. However, we believe that it may still prove useful for practicing clinicians. Since the association of sarcoidosis with chylothorax is exceedingly rare, alternative etiologies should be pursued even when chylothorax develops in a subject with preexisting sarcoidosis. On the other hand, chylothorax might be part of the initial presentation of sarcoidosis. When other etiologies for a newly diagnosed chylothorax are ruled out, the possibility of sarcoidosis should be entertained, as it may lead to therapeutic implications. A Multidisciplinary approach is required for optimal management, both for elucidating the diagnosis and for employing therapy, which could be multimodal. A trial of immunosuppressive therapy with corticosteroids should be considered.

In conclusion, we provide a review of the published literature regarding cases of sarcoidosis-associated chylothorax and suggest pathophysiological mechanisms. While it is an extremely rare condition, we hope that this review might help guide management of similar patients.

Conflicts of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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