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Original contribution

Chronic follicular pleuritis: a B cell–rich form of nonspecific pleuritis/fibrosis☆,☆☆

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Summary The parietal pleura is often biopsied in patients with idiopathic pleural effusion, and in up to 40% of cases, a diagnosis of nonspecific pleuritis/fibrosis (NSP) is rendered. The histology of this reaction has not been well described including a pattern of B cell lymphoid hyperplasia described as "chronic follicular pleuritis (CFP)". Thirty-two cases of NSP were studied, of which 13 (41%) corresponded to CFP with the remainder displaying a fibrinous and organizing pleuritis with varying degrees of collagenization. CFP had similar etiologies as NSP with long term follow-up, including cardiac disease, pericarditis, asbestos exposure, and occult malignancy. The importance of recognizing a previously undescribed B cell/plasma cell pleural inflammatory response in reactive pleural disease is discussed.

1. Introduction

Patients with idiopathic pleural effusion often undergo needle or thoracoscopic biopsy for diagnostic purposes. Somewhere between 10% and 40% of cases will have a nondiagnostic pleural biopsy that is usually classified as "nonspecific pleuritis/fibrosis (NSP)" [1-12]. This term, widely used in the clinical literature, encompasses a variety of pathologic diagnoses including "fibrinous pleurisy", "fibrous pleurisy", "reactive pleural fibrosis", "florid reactive change", "chronic inflammation", "dense fibrous tissue" among others [1,2,6,10,11]. These monikers apply when no malignancy, granulomatous disease, pleural vasculitis, or bacterial or fungal infection is identified at time of biopsy. NSP is most often associated with an exudative pleural effusion, rich in T cells when subjected to flow cytometric and immunohistochemical analysis [13-17].

In a provisional review of 32 cases of nonspecific pleuritis with idiopathic pleural effusion, I identified a pattern of pleural inflammation that can be termed "chronic follicular pleuritis (CFP)". CFP manifested as a pleural inflammatory process with micronodules of reactive lymphoid follicles with germinal centers, fused by a dense band of small round lymphocytes and plasma cells within the pleural soft tissue. In contrast to being dominated by T cells, this infiltrate was B cell rich and was not clonal. This paper describes the clinical and pathologic characteristics of non-specific pleuritis/pleurisy and the distinct subset of B cell and plasma cell predominant chronic follicular pleuritis.

2. Materials and methods

The surgical pathology files of the University of Pittsburgh Medical Center from 2003 to 2018 were searched for pleural

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biopsies that had been characterized as chronic pleuritis, chronic fibrous pleuritis, fibrous pleurisy, fibrinous pleurisy, fibrous pleuritis, organizing pleuritis, nonspecific pleuritis, and lymphocytic pleuritis, and had been cross linked with a clinical diagnosis of idiopathic pleural effusion. Thirty-two cases were identified for which slides and blocks were available. The medical records of these 32 cases were then reviewed to determine a cause of this reaction and to investigate the clinical presentation, radiographic findings, and clinical outcome related to the patient's pleural disease. Data was collected through the institutional network Cancer Registry and the study was conducted under an exemption approved by the University of Pittsburgh Institutional Review Board (PRO 12070229).

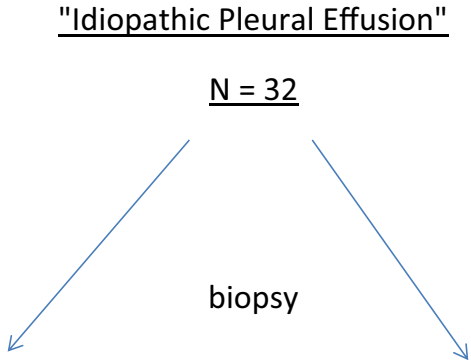
All biopsies that displayed a metastatic or primary malignancy, eg, metastatic carcinoma, lymphoma, or malignant mesothelioma, granulomatous disease, purulent exudate suggesting infection, eosinophilic pleuritis due to pneumothorax, or extensive hemorrhage were excluded from this analysis. Grocott stains (N = 31) and acid fast stains (N = 8) were negative in all cases as were microbiologic culture studies in 30 cases. B cell gene rearrangement studies were done on biopsy tissue in 6 cases and failed to show heavy or light chain rearrangements. Flow cytometry was not done on pleural fluid in the 32 cases for review. In all 32 cases immunohistochemical studies for CD3, L26/CD20, CD5, cyclin D1, CD43, κ and λ light chains were performed as previously described [18,19].

3. Results

Of the 32 cases identified, 19 patients with parietal pleural biopsies fell into the aforementioned category of nonspecific pleuritis/fibrosis (Fig. 1). Eleven were men; 8 women. Average age was 60.5 years (median; 62 years; range 23–85 years). Clinical symptoms were shortness of breath (N = 9; 47%), dyspnea on exertion (N = 7; 37%), cough (N = 4; 21%), chest pain (N = 4; 21%) and weight loss (N = 2; 11%). Three patients had no complaints and were identified on routine examinations. A smoking history was present in 12 (63%). Two patients had a history of asbestos exposure. Eight had a negative PPD study. Two patients had a history of auto-immune disease (Sjogrens syndrome, Graves' disease).

Chest computed tomographic scans showed a unilateral pleural effusion with pleural thickening in 15 cases (8 right, 7 left) and bilateral effusions were seen in 4 (21%) patients. At last follow-up (average, 34 months; median, 42 months; range, 2-104 months), 4 patients (21%) had recurrent disease, while 15 (79%) patients had no evidence of recurrence and were currently free of effusions. All effusions were exudative and pleural fluid cytologies on all were benign.

Longitudinal follow-up of the 19 patients with NSP and clinical idiopathic pleural effusion resulted in an ultimate clinical determination of etiology in 11 cases: post irradiation for Hodgkin Lymphoma (N = 2); metastatic adenocarcinoma (N = 2—lung and cholangiocarcinoma), asbestos pleuritis



"Nonspecific pleuritis"

N = 19

At followup:

Etiology identified: 11

Idiopathic: 8

"Chronic follicular pleuritis"

N = 13

At followup:

Etiology identified: 7

Idiopathic: 6

Fig. 1 Idiopathic pleural effusion.

(N = 1), cardiac disease (N = 4), liver failure (N = 1), and infection (N = 1). Eight cases were felt to be idiopathic.

Thirteen patients (41%) of the study cohort of 32 were classified as chronic follicular pleuritis (CFP). CFP was seen primarily in elderly men (male/female—10/2; mean age, 69.3 years, median, 73 years; range, 50–85 years) who presented with shortness of breath (N = 6, 46%), dyspnea on exertion (N = 6, 46%), cough (N = 5, 26%), weight loss (N = 3, 16%), and chest pain (N = 2, 11%). A smoking history was present in nine of 13 (69%). One patient had a history of autoimmune disease (primary biliary cirrhosis) and 2 had a history of asbestos exposure. PPD was negative in 12 patients.

Eleven of the 12 patients had unilateral pleural effusions with pleural thickening (right, 7; left, 4) and 1 patient had bilateral pleural effusions. In all 12 cases the pleural fluid was exudative. Cytologies were negative for malignant cells in all cases.

Clinical follow-up was obtained in all 13 cases (mean, 37.8 months; median, 42 months; range, 3–156 months). In 3 cases (23%) pleural fluid reaccumulated and needed to be drained. At last follow-up, no patient had evidence of persistent pleural effusion although all showed subtle evidence of mild pleural thickening. In 7 (54%) cases, a clinical etiology for the CFP was ultimately identified: constrictive pericarditis (N = 2), metastatic lung adenocarcinoma (N = 2), chronic congestive heart failure/Dressler's syndrome (N = 2), and asbestos pleuritis (N = 1). Six cases (46%) were idiopathic.

4. Histopathology

Thoracoscopic parietal pleural biopsies were performed in all cases and the pleural surface was variously described by surgeons as demonstrating either “local or diffuse thickening of the pleura”, “nodular change of the pleural surface’, or “diffuse inflammation”, for example.

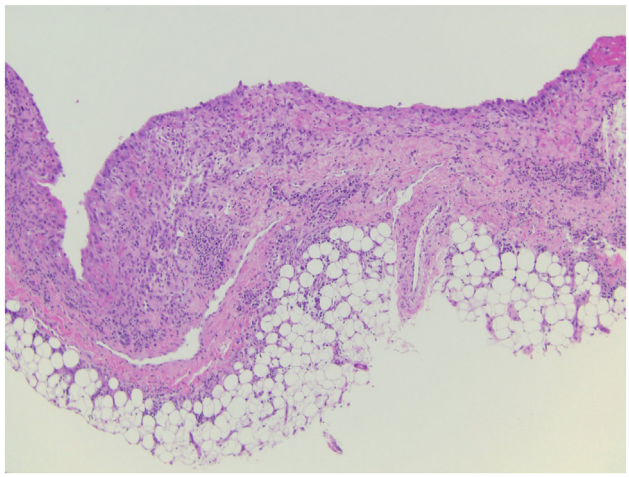


Fig. 2 Nonspecific pleuritis/fibrosis: biopsies displayed a fibrinous and organizing pleuritis with a stromal granulation tissue reaction and collagenization (H&E, original magnification ×40).

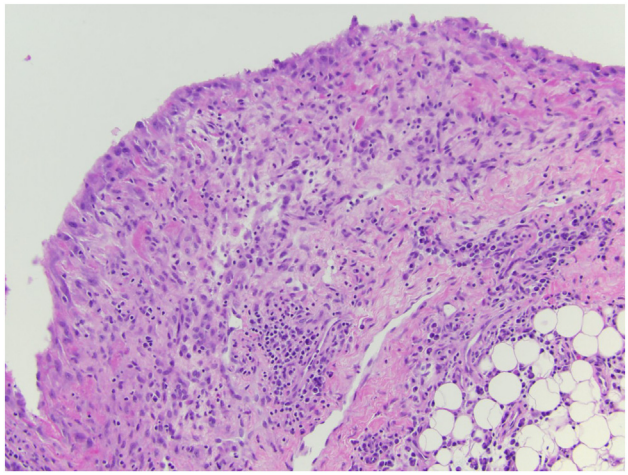


Fig. 3 Nonspecific pleuritis/fibrosis: reactive mesothelial cells line inflamed submesothelial connective tissue with a granulation tissue-like admixture of reactive myofibroblasts, endothelial cells and scattered chronic inflammatory cells (H&E, original magnification ×100).

The 19 cases of nonspecific pleuritis/fibrosis (NSP) in this study manifested as a fibrinous and organizing pleuritis in 6 cases (32%), fibrinous and organizing pleuritis superimposed on a chronic fibrous pleuritis in 7 cases (37%) and as a chronic fibrous pleuritis in 6 cases (32%). Fibrinous and organizing pleuritis reflected a layer of fibrin and loose granulation tissue coating the pleural surface accompanied by mesothelial cell hyperplasia (Figs. 2 and 3). Hemosiderin was seen in 3 cases. A patchy diffuse nonlocalized chronic inflammatory cell infiltrate consisted primarily of small round lymphocytes and rare neutrophils and eosinophils. In 7 cases this reaction appeared superimposed on a diffuse background of fibrous scarring of the parietal pleura that lacked characteristics of a hyaline pleural plaque. In 3 cases, aggregates of round lymphocytes clustered around small venules, but lacked germinal center

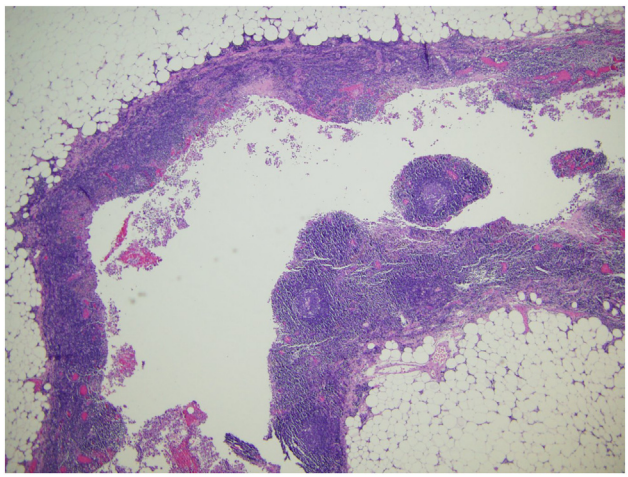


Fig. 4 Chronic follicular pleuritis: a dense bandlike infiltrate of chronic inflammatory cells expands the pleura and trickles into adipose tissue. Scattered germinal centers are seen (H&E, original magnification ×20).

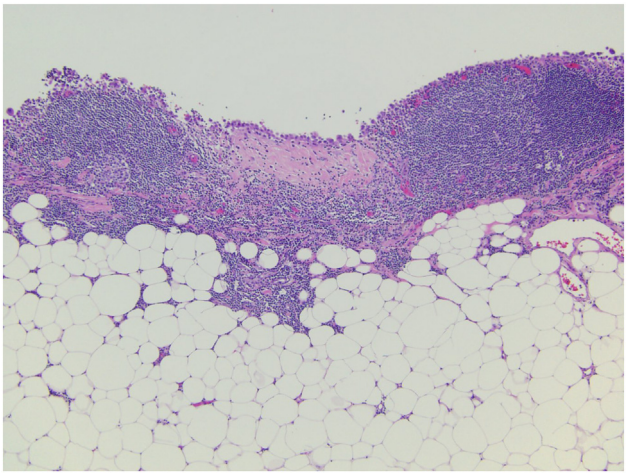


Fig. 5 Chronic follicular pleuritis: the dense submesothelial lymphocytic infiltrate was associated with interrupted bands of dense collagen and germinal centers at right (H&E, original magnification ×100).

formation. In 6 cases (32%), the morphology was that of a chronic fibrous pleuritis with a diffuse irregular submesothelial scar with a patchy mild chronic inflammatory infiltrate of small round lymphocytes and plasma cells. Eosinophils and neutrophils were scant.

Immunostains showed that the mononuclear cell infiltrate was largely CD3 positive T cells with the perivascular mononuclear cells represented by a mixture of T cells, CD20 B cells, and plasma cells. No co-expression of CD20, CD5, or CD43 was seen by the mononuclear cells. Cyclin D1 was not expressed. No CD10 or BCL6 positive germinal center cell lymphocytes were noted.

Histologically the 13 cases of CFP were characterized at low magnification by a bead-like infiltrate of large reactive lymphoid follicles with secondary germinal centers, with an intervening band of mononuclear cells, juxtaposed to

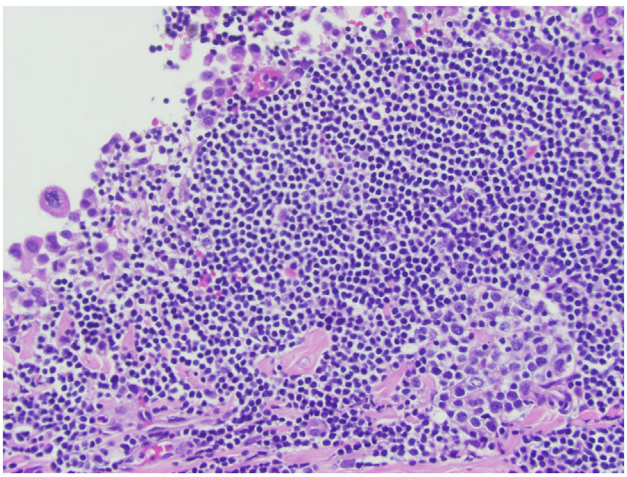


Fig. 6 Chronic follicular pleuritis: reactive lymphoid follicles with prominent germinal centers peppered the dense mononuclear infiltrate accompanied by reactive mesothelial hyperplasia (H&E, original magnification ×200).

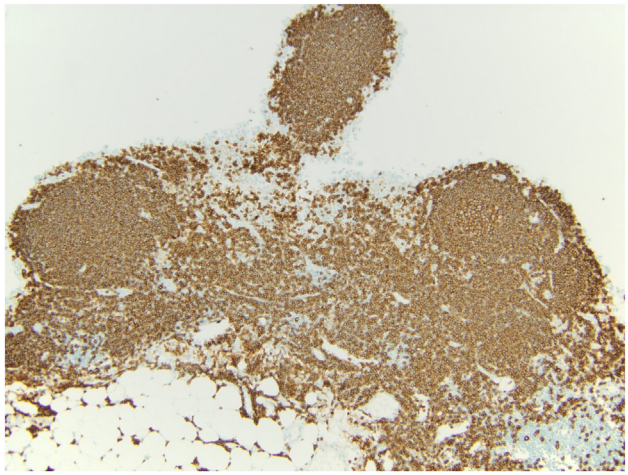


Fig. 7 Chronic follicular pleuritis: B cells dominated the inflammatory infiltrate with CD20 stains (immunoperoxidase, CD20, original magnification ×100).

subpleural adipose tissue (Fig. 4). This lymphoid infiltrate was usually covered by a continuous (N = 10, 77%) or interrupted (N = 3, 23%) layer of dense fibrous scar tissue that apposed the pleural cavity. Lymphocytes percolated through this scar tissue in the majority of cases (Figs. 5 and 6). A superimposed fibrinous and organizing pleuritis was seen along the pleural cavity surface in 5 cases (38%), usually accompanied by hemosiderin deposits and reactive mesothelial cell hyperplasia. In 3 cases (23%) hyaline pleural plaques were present. In no instance was there evidence of malignant mesothelioma or malignant lymphoma.

Immunostains showed that the lymphoid aggregates were largely B cells and that their mantle and marginal zones often fused with that of the adjacent lymphoid follicles forming a confluent band of CD20 positive mononuclear cells, primarily small round lymphocytes, and monocytoid cells, and admixed plasma cells (Fig. 7). These B cell follicles contained a rich spider web

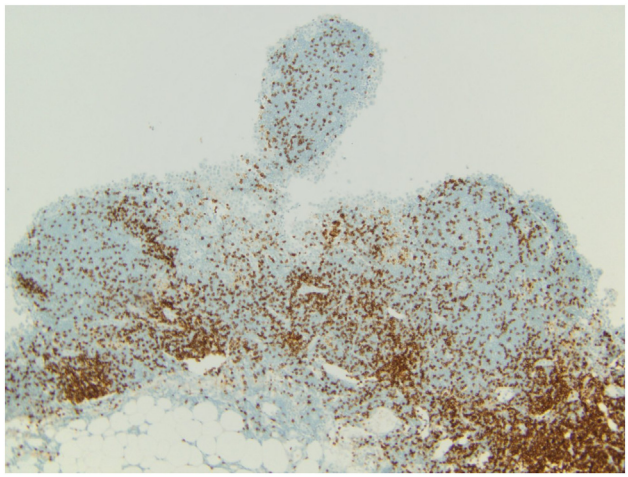


Fig. 8 Chronic follicular pleuritis: T cells were present in equal or diminished number to B cells with CD3 stains (immunoperoxidase, CD3, original magnification ×100).

like network of dendritic cell processes with CD21 stains reflecting preserved follicular immunoarchitecture. CD3 positive T cells surrounded the B cell follicles and in regions where follicles were not juxtaposed, the T cells were part of the linear bands between the follicles, admixed with B cells (Fig. 8). No co-expression of CD5 or CD43 by L26/CD20 positive B cells was seen. Cyclin D1 stains revealed normal mantle cells but did not highlight any monotonous population of lymphoid cells in any of the cases. κ and λ immunostains showed a polytypic population of plasma cells. As noted in the materials and methods, gene rearrangement studies on the biopsy material failed to show a clonal population of B or T cells in 6 cases. EBER studies for Epstein Barr virus were negative in 6 cases.

5. Discussion

The clinical terms "idiopathic pleural effusion" and its pathologic analog "nonspecific pleuritis/fibrosis" are often applied to the static clinical presentation of a unilateral exudative pleural effusion of unknown etiology with biopsy changes that are also not diagnostic [1,2]. However, when this clinical condition is observed over time, a specific etiology for the effusion and histologic changes becomes evident in between 60 and 80% of cases [1-3,6,7,10-12]. The most common postbiopsy causes include the following: tuberculosis, malignant mesothelioma or metastatic carcinoma, asbestos pleural diseases, heart failure, liver cirrhosis, postradiation effusion, trauma, parapneumonic effusion, and autoimmune disease. Most important is malignancy which occurs in between 8 and 20% of the cases probably as a consequence of a failure to sample diagnostic tissue [1-3,6,7,10-12,20,21]. Persistence of the effusion, weight loss, fever, and large size of the effusion usually are harbingers of a subsequent malignant diagnosis [20]. In many reports where patients had asbestos exposure, biopsies were done to exclude mesothelioma [1,3]. This occurred in 2 of our cases.

A common historic cause of nonspecific pleuritis is tuberculosis [7,10,11,15,22]. In cases with this suspected diagnosis, many pulmonologists choose to empirically treat for mycobacterial infection although this option is less often utilized than in the past.

The remaining 20–42% of cryptogenic pleural effusions with nonspecific pleuritis occur in older men, primarily as a unilateral exudative pleural effusion, rich in T cells which resolve after thoracoscopic biopsy in between 64 and 90% of cases [1,2,6,7,10-12]. While there is a significant clinical literature on idiopathic pleural effusion, there has been no systematic review of the parietal pleural biopsy changes in this condition beyond listing fibrinous/organizing or chronic pleuritis with fibrosis, and an association with T cell predominant pleural effusion [13,14,16,17]. In nonmalignant reactive pleural effusions, T cells, macrophages, NK cells and eosinophils dominate the cell population of the pleural fluid [23-26]. CD4 positive T cells predominate over CD8 positive cells, while B cells and plasma cells comprise less than 5% of the cells in effusion exudates [23].

I reviewed 32 clinical cases of nonspecific pleuritis/fibrosis (NSP). As noted, the majority had very prosaic histologies without specific histologic findings. However, 13 of the 32 cases (41%) had a distinctive histopathology of chronic follicular pleuritis. On longitudinal follow-up, an etiology could be identified clinically in 6 of these 13 CFP cases—metastatic carcinoma, congestive heart failure, constrictive pericarditis, and asbestos exposure—similar to cases of NSP. Seven cases remained idiopathic. When the study began, I suspected that CFP would have an association with autoimmune disease or allergic phenomena. This was not found. The etiologies for CFP were similar to NSP. CFP then seems to represent a nonspecific pleural reaction that has a prominent B cell component in its inflammatory profile, likely to be idiosyncratic and unique to each individual. Second, the morphology and cellular infiltrates suggested a B cell immune reaction contrasting with the consistent reporting of a T cell predominant effusion based on flow cytometry in idiopathic pleural effusions/nonspecific pleuritis [23-26]. While certainly T cells were present in the biopsy, B cells predominated in most cases. This finding seemed to indicate that in chronic inflammation of the pleura the endogenous B cell lymphoid tissue along the lymphatics of the parietal pleura becomes hyperplastic in addition to the T cell inflammatory response. It also suggests that T cells are more likely to traverse the parietal mesothelium into the pleural cavity for unknown reasons thus accounting for the literature indicating that nonspecific pleuritis is associated with T cell rich effusions [23,27,28]. This impression is indirectly supported in that over one third of our cases of NSP were B cell rich i.e. CFP. One would suspect, by implication, that some of these studies of the cell profile of idiopathic pleural effusion would have noted a prominent B cell component if these B cells were migrating into the pleural cavity into the effusion exudate. This B cell reaction may also be similar to some organs where B cell, rather than T cell, hyperplasia occurs in response to antigenic stimulation, eg, diabetic mastopathy, autoimmune sialoadenitis.

The intensity of the B cell infiltrate and the focus on T cells in pleural disease highlights the need to separate CFP from pleural involvement by malignant lymphoma especially mucosa associated marginal zone B cell lymphoma and small lymphocytic lymphoma. This distinction can be made through immunohistochemical testing, flow cytometry on biopsy and effusion specimens and gene rearrangement studies.

While CFP has a distinctive morphology, its biology appears similar to idiopathic nonspecific pleuritis [1,2,9]. Only 30% of cases had recurrent pleural effusion and the majority resolved within 18 months with minimal residual pleural thickening [11,12].

This study has the intrinsic limitations of a retrospective study. Pleural fluid was not subjected to flow cytometry for cell typing and quantitation in any of our cases. Cultures were negative in all cases when performed, and silver stains were done on all cell cytospins to exclude fungal and pneumocystis infection. Gram and acid fast stains were not performed uniformly.

In summary, this study describes a B cell–rich variant of pleuritis, chronic follicular pleuritis that represents a distinct histologic manifestation of clinical idiopathic nonspecific pleuritis that can be confused with malignant lymphoma, and represents a pleural reaction not typically identified or described in nonspecific pleuritis.

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