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Organizing pneumonia associated with Richter transformation in chronic lymphocytic leukemia: a case report and review of the literature

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Abstract: Organizing pneumonia (OP) is defined histologically by the presence of granulation tissue within alveolar ducts and alveoli. Recently, several lymphoid neoplasms have been implicated as a risk factor for OP, however, OP as a primary manifestation of malignancy transformation has not been widely reported in the literature. Here, we report a case of a patient with a history of chronic lymphocytic leukemia (CLL) who presented with weight loss, low-grade fever, lymphadenopathy, and bilateral pulmonary infiltrates revealed in imaging studies. Video-assisted thoracoscopic lung biopsy showed CLL cells within the pulmonary vessels and areas of OP in the lung parenchyma. Subsequent lymph nodes biopsies were consistent with CLL transformation to diffuse large B-cell lymphoma (DLBCL). To our knowledge, this is the first reported case of OP associated with CLL transformation into DLBCL. This case suggests that OP could represent a form of immunological reaction to ongoing Richter transformation.

Keywords: organizing pneumonia, pulmonary infiltrates, chronic lymphocytic leukemia, Richter transformation.

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Introduction

Organizing pneumonia is classified as a form of Idiopathic Interstitial Pneumonia [1] and defined histologically by the presence of granulation tissue within the distal alveolar ducts and alveoli [2, 3]. The secondary form of OP has been reported in the course of multiple conditions, including connective tissue disorders, infections, aspiration pneumonia, adverse drug reactions, neoplasms, or allogeneic hematopoietic cell transplantation (allo-HCT) [2–4]. Cryptogenic organizing pneumonia (COP) refers to the idiopathic form of OP which cannot be linked to a specific condition [1–3].

Patients with hematologic malignancies are more likely to develop OP, mainly due to a broad range of infectious complications [5, 6]. Other potential risk factors involve the receipt of chemotherapy and biological agents, treatment with allo-HCT or radiotherapy [7, 8]. More recently, several lymphoid neoplasms, comprising acute lymphoblastic leukemia, chronic lymphocytic leukemia (CLL) and other non-Hodgkin lymphomas (NHLs), or Hodgkin lymphoma have been implicated as a risk factor for OP [7, 9, 10]. However, OP as a primary manifestation of malignancy transformation has not been widely reported in the literature.

Here, we report a rare case of COP in a patient with CLL without a history of recent treatment which preceded Richter transformation (RT) into diffuse large B-cell lymphoma (DLBCL).

Case report

In September 2020, a 65-year-old male patient was referred to the Department of Hematology for the evaluation of multiple, pulmonary infiltrates and lymphadenopathy identified in imaging studies. Past medical history was significant for CLL diagnosed in 2011, previously treated with chlorambucil and prednisone, which remained in remission since 2013.

The patient presented with a five-month history of chest pain, malaise, and weight loss exceeding ten kilograms. Imaging studies demonstrated multiple bilateral consolidations with subpleural distribution (Fig. 1A) accompanied by widespread lymphadenopathy. Given the high suspicion of lung metastases from a distant tumor, he was initially followed up at the Department of Oncology. Axillary lymph node biopsy was obtained for the cytological examination which showed a predominance of lymphoid cells with clumped chromatin, occasional prolymphocytes and paraimmunoblasts, suggestive of small lymphocytic lymphoma (SLL) and corresponding to the nodal equivalent of CLL. Blood investigations, whole-body computed tomography (CT), and colonoscopy did not show features indicative of a primary tumor. To obtain the specimens from the consolidation area, the patient subsequently underwent a video-assisted thoracoscopic lung biopsy, which demonstrated fibroblastic deposits and inflammatory plugs in alveolar ducts and alveoli, histologically consistent with organizing pneumonia (Fig. 2). Neoplastic cells were not visualized in the areas with OP, but diffuse subpleural lymphocyte infiltration was noted, immunohistochemically (IHC) characterized by CD20+, PAX5+, CD5+, CD23+, FOX-P1+ reactions and corresponding to CLL lymphocytes.

As the progression of CLL was suspected, the patient was referred to the Department of Hematology for further evaluation. High-resolution CT (HRCT) of the chest performed on admission exhibited ground-glass opacities with a new, dominant left upper lobe lesion in the periphery (Fig. 1B–E), however, a marked overall regression of the infiltrates was observed. Blood tests showed elevated lymphocyte count (4.3×10^9/l), although not fulfilling the diagnostic criteria for CLL, defined as a monoclonal B-cell count $\geq 5 \times 10^9$/l with the characteristic morphology and phenotype

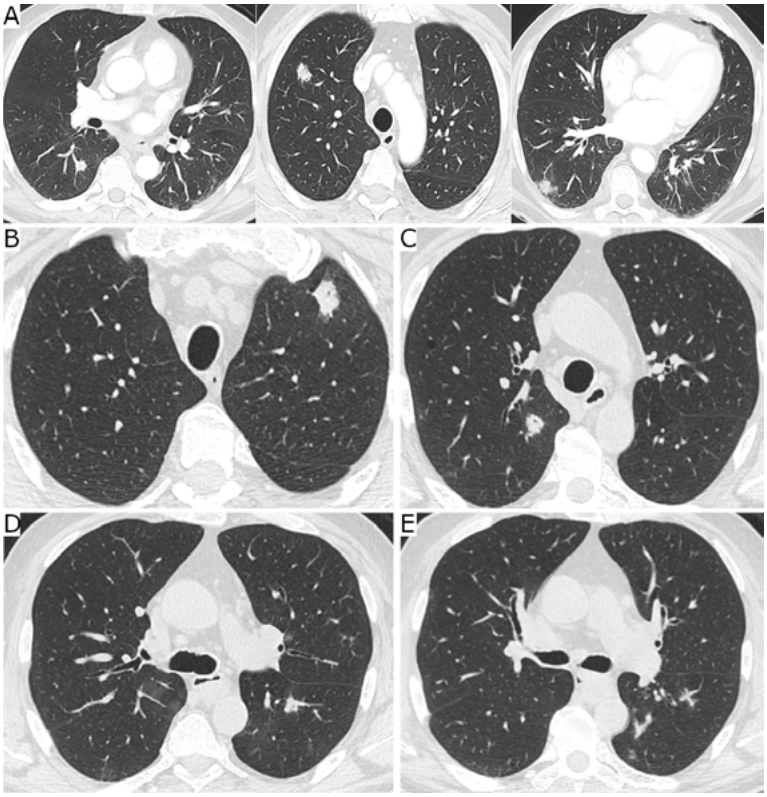

Fig. 1. (A) Chest scan (lung window) showing multifocal and asymmetrical parenchymal consolidation with peripheral and subpleural distribution and nodular consolidation with ground glass opacification. (B–E) High-Resolution Computed Tomographic imaging (lung window) showing new consolidation with air-bronchogram (B, C) and nodular consolidation (D, E).

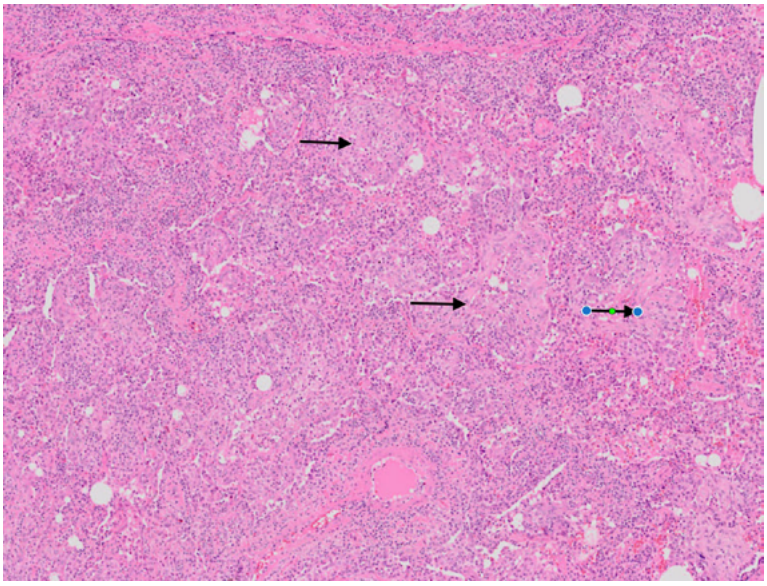

Fig. 2. Microphotograph, hematoxylin and eosine stain, low magnification. Organizing inflammatory exudate fills the lumen of the alveoli. A diffuse, chronic, lymphoid inflammatory infiltrate is seen in the surrounding stroma of the lung. The interstitium is mildly thickened.

of CLL in the peripheral blood. Laboratory tests ruled out, among others, viral, fungal, bacterial pneumonia, or tuberculosis. The previously collected lung specimen was sent for pathological reassessment. Evaluation for infection, including fungal stains and Ziehl–Neelsen stain for acid-fast bacilli was unremarkable. CD20+, PAX5+, CD5+, CD23+ lymphocytes, corresponding to CLL cells were found to be confined to vessels and no direct pulmonary involvement by leukemic cells was identified. Based on radiological and pathological findings and given no definite cause, the diagnosis of cryptogenic organizing pneumonia was established. As the pulmonary lesions partially self-resolved, corticosteroid treatment was not initiated, and the patient was discharged home.

The follow-up PET-CT scan performed 2 months later showed progressive abdominal and mediastinal FDG-avid lymphadenopathy. Lymph node biopsy revealed CLL/SLL cells and diffuse sheets of large B cells with immunophenotype compatible with DLBCL, not otherwise specified. The diagnosis of RT was confirmed and the treatment with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) chemoimmunotherapy was initiated, resulting in a complete metabolic response at the end of treatment.

Discussion

Organizing pneumonia preceding the diagnosis of lymphoid neoplasm has been previously described in the literature [7, 11–14], however, its link with malignancy progression has been only occasionally reported [15, 16]. To the best of our knowledge, this is the first reported case of OP associated with CLL transformation into DLBCL, NOS.

The development of OP in patients with lymphoid neoplasms is most commonly reported in the setting of previous exposure to systemic treatment, including radiation and chemotherapy [7, 17]. More than 35 drugs were found to be linked with OP and antineoplastic agents represent a substantial part of the known causes, including rituximab [18], chlorambucil [19], bleomycin, doxorubicin, and others [17].

Although OP is a rare cause of pulmonary findings in patients with hematologic malignancy [20, 21], it should be considered in individuals who present with non-specific clinical symptoms and radiological abnormalities [20, 21]. Since it is not possible to differentiate between OP and a variety of infectious and inflammatory etiologies based on non-invasive methods, a biopsy is generally required to establish an accurate diagnosis [2, 3]. Despite the higher risk of complications, a surgical biopsy is considered the most reasonable diagnostic approach, as it provides an adequate specimen size and allows to rule out differential diagnoses [2, 3]. Infectious processes and secondary malignant infiltrates are ruled out through serological tests, cultures, bronchoalveolar lavage fluid examination, and histological examination with IHC staining of the tissue [2, 3].

In the presented case, there was no history of recent treatment which could potentially induce the development of OP. We therefore speculated that OP could represent a form of immunological reaction to ongoing RT manifested by progressive lymphadenopathy. Polaczek *et al.* have previously reported the development of OP in a patient with CLL/SLL associated with progression to mixed B-cell NHL [16]. Authors concluded that the inflammatory process in lung parenchyma was most likely due to the increasing number of abnormal leukemic cells. Keaton *et al.* recently described a similar case of histologically proven OP in a patient with CLL with increasing lymphocyte counts [22]. We suggest that, in these cases, OP might work as a paraneoplastic syndrome accompanying CLL transformation. This possibility is further supported by previous reports on OP preceding the development and diagnosis of lymphoid malignancy (Table 1). Although this

Table 1. Summary of previous reports of OP associated with diagnosis of lymphoid malignancy.

Reference	Primary malignancy	Presenting symptoms	Lung biopsy technique used for histological confirmation of OP	Time of biopsy-proven OP diagnosis as compared to malignancy diagnosis	Treatment (initial dose) of OP and outcome	Treatment of the underlying malignancy and outcome
Chan 2020 [12]	Enteropathy associated T-cell lymphoma	Fever, productive cough, hemoptysis	TBB, CT-guided TTB	9 months prior	Prednisone (50 mg); one relapse treated with second course of steroids (response to treatment not specified)	No treatment; death from hemophagocytic lymphohistiocytosis secondary to lymphoma at nine months
Lal 2018 [11]	Hodgkin lymphoma with localized extranodal lung involvement	Dry cough, vomiting, chest discomfort, hemoptysis	Open lung biopsy	4 months prior	Prednisone (60 mg); recurrence of symptoms while on tapering dose of prednisone; resolution following the treatment of the lymphoma	ABVD and radiotherapy; complete remission at 7 years
Bordas-Martinez 2019 [13]	DLBCL; Hodgkin lymphoma diagnosed in post-mortem examination	Low-grade fever, dry cough, dyspnea	VATS lung biopsy	15 years prior	Prednisone (15 mg); Mycophenolate mofetil; Intravenous immunoglobulin therapy; steroid-dependent disease, multiple relapses	Rituximab monotherapy (due to poor performance status); death from sepsis after third dose
Barnes 2016 [24]	DLBCL with localized extranodal lung involvement diagnosed in post-mortem examination	Dry cough, dyspnea	TBB	Months before diagnosis of DLBCL in autopsy	Corticosteroids (not specified); minor response with progression of the symptoms	No treatment; death from acute respiratory failure
Sela 2018 [14]	Pulmonary extranodal marginal zone lymphoma	Fever, cough, malaise	TBB, VATS lung biopsy	Concomitant diagnosis of OP and lymphoma	Corticosteroids; complete resolution of the pulmonary findings	Rituximab monotherapy; in remission at last follow up (follow up duration unknown)
Polaczek 2015 [16]	CLL/SLL, transformation into mixed B-cell non-Hodgkin lymphoma (not specified)	Fever, productive cough, dyspnea, fatigue	Open lung biopsy	8 months after diagnosis of CLL; concomitant diagnosis of OP and CLL progression	Prednisone; complete resolution of the pulmonary lesions, no relapse at 9 months	No treatment; in clinical remission at last follow up (follow up duration not known)
Zeldin 2005 [23]	Follicular lymphoma	Fatigue, weight loss, dyspnea	Lung biopsy (not specified)	Concomitant diagnosis of OP and lymphoma	No treatment	Chemotherapy (CVP protocol); lost to follow up
Safadi 1997 [25]	Primary pulmonary B-cell non-Hodgkin lymphoma (not specified)	Productive cough, dyspnea, malaise, weight loss, night sweats	CT-guided TTB, TBB, open lung biopsy	6 months prior	Hydrocortisone (300 mg); one relapse successfully treated with second course of steroids	Chemotherapy (CAP protocol); died due to pneumonia three months later

Abbreviations: TBB — transbronchial biopsy; TTB — transthoracic biopsy; VATS — video-assisted thoracoscopic surgery; CT — computed tomography; DLBCL — diffuse large B-cell lymphoma; ABVD — doxorubicine, bleomycin, vinblastine, dacarbazine; CLL/SLL — chronic lymphocytic leukemia/small lymphocytic lymphoma; CVP — cyclophosphamide, vincristine, prednisone; CAP — cyclophosphamide, doxorubicin, prednisone.

phenomenon is rare, the available literature suggests that OP may occur from up to 15 years to 4 months prior to the recognition of neoplasm [13, 23]. In two cases, the diagnosis of concomitant OP and NHLs was made on initial presentation [14, 23]. In the remaining patients who were initially diagnosed with OP, the tendency for relapses on corticosteroid treatment indicates that the underlying malignancy could be missed on primary biopsy due to inadequate tissue sampling [11–13, 24]. OP was diagnosed both in primary pulmonary lymphomas and neoplasms not involving pulmonary tissue [11, 14, 24, 25].

An interesting observation in the presented case is that clinical and radiological signs partially resolved without treatment. Systemic corticosteroid therapy represents the first-line approach in symptomatic OP and usually leads to rapid regression of the lesions within days to weeks [2, 3]. While treatment is necessary in most cases, the self-limiting disease is observed only in a small subset of patients [3]. In our patient, pulmonary lesions resolved spontaneously before the diagnosis of RT was established, whereas the management of secondary OP generally requires treatment of the underlying disease [2]. Hence, we cannot rule out the idiopathic form of OP (COP), which developed independently from CLL transformation.

In summary, this case highlights the unusual association of OP with Richter transformation in the course of CLL/SLL and supports the previous reports on OP as a harbinger of neoplasm. The possible mechanism linking OP and lymphoid malignancies is yet to be established, however, we hypothesize that OP might represent an aberrant immune response to malignancy.

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Conflict of interest

None declared.

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