

Characteristics and Follow-Up of Organizing Pneumonia Associated with Hematologic Malignancies

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Abstract

Background: Organizing pneumonia (OP) is a secondary process in many diseases. Due to low incidence and indistinct symptoms, there is limited information about OP associated with hematologic malignancies. To discuss the characteristics and prognosis of OP associated with hematologic malignancies, we conducted this study.

Methods: We observed and analyzed pathologically confirmed OP cases associated with hematologic malignancies in hospital records database, and excluded OP cases with other related reasons, including chemotherapy, radiotherapy, targeted therapy, transplantation and infection.

Result: There were 5 patients with OP underlying only hematologic malignancies, including one case of myelodysplastic syndrome, one case of acute myelogenous leukemia, one case of multiple myeloma case, one case of aplastic anemia, and one T cell lymphoma. Radiological findings did not show a distinct pattern, and two cases mimicked pulmonary aspergillosis. The diagnosis of OP was confirmed by minimally invasive biopsy. Although all patients developed into severe cases, steroids produced favorable outcomes.

Conclusion: This study supports that hematologic malignancies might be a cause of OP and that minimally biopsy may be an effective and safe method to confirm the diagnosis. Although OP associated with hematologic malignancies might more frequently develop into severe cases, the OP lesions were steroid-responsive during follow-up.

Introduction

Organizing pneumonia (OP) is defined distinctively as filling of the distal air spaces with buds of granulation tissue progressing from fibrin exudates to loose collagen containing[1]. This pathologic pattern may be encountered in different disease processes, such as infection, infraction, special treatments (e.g., chemotherapy) and immune disorders (e.g., connective tissue diseases and graft-versus-host disease)[2, 3]. According to its causes or associated diseases, OP can be categorized into OP with a determined cause, OP with undetermined causes but underlying specific or relevant conditions and cryptogenic OP (COP). Unfortunately, there is a lack of distinct features among these three groups[2]. The clinical characteristics of OP are similar to those of respiratory infection (with recurrent or persistent fever, dyspnea, cough, and weakness as the dominant symptoms), and are difficult to differentiate from other pathologic processes. The radiologic manifestations are also non-specific, exhibiting patchy consolidation and “ground-glass” opacities. The potentially significant features might be migrating pulmonary infiltrates and less pulmonary fibrosis during follow-up[2].

The common pulmonary complications of hematological malignancies are infectious diseases and might be frequently attributed to immune deficiency[4, 5]. However, noninfective causes, such as pulmonary edema, hemorrhage, autoimmune manifestations and pulmonary alveolar proteinosis, could be potential etiologies for pulmonary infiltrates in patients with hematological malignancies [3–5]. In the last decade, OP has been reported in hematologic disorders patients[3, 6–8]. Other related factors, including chemotherapy, stem cell transplantation (SCT) and infection, have been previously described with respect to OP in case of hematological malignancies[3, 7]. Therefore, there were limited information about OP underlying only hematologic malignancies, or caused by hematologic malignancies. Moreover, due to the lack of specific features, it is difficult to distinguish OP from other pulmonary complications in hematological malignancies. To discuss OP associated with hematological malignancies, excluded other related reasons, we conducted this observational study.

Materials And Methods

Study design

This observational study was performed at a 3500-bed tertiary teaching hospital, the Second Xiangya Hospital of Central South University, Changsha, in mid-southern China. This study was approved and supervised by the Medical Research Ethics Committee of the Second Xiangya Hospital, Central South University. Written informed consent was waived. The hospital records database was searched for all cases of OP with hematologic malignancies from 1 January 2000 to 1 July 2020. The diagnosis of OP was confirmed by two independent pathologists following the American Thoracic Society/European Respiratory Society statement (2013 update)[9]. Patients were excluded if they had other related conditions, including chemotherapy, radiotherapy, targeted therapy, SCT, bone marrow transplantation (BMT), cord blood transplantation (CBT) and infection.

To exclude infection, sputum, bronchoalveolar lavage fluid (BALF), blood and bone marrow cultures were conducted in these patients, none of which produced positive results. 1, 3- β -D-Glucan (G) and galactomannan (GM, both in blood and BALF) tests also did not show positive results. Interstitial lung diseases (ILDs) induced by connective tissue disease (CTD) were excluded by antigen and antibody detection for CTD.

The following medical information was examined: demographics, underlying cancer diagnoses, physical examination and laboratory findings, pulmonary function before OP diagnosis, findings on chest radiography and computed tomography (CT), steroid treatment, use of concurrent treatments, clinical outcomes and follow-up.

Definitions

The duration of OP diagnosis was defined as the time from symptom onset to the pathologic diagnosis of OP. Clinical outcomes were confirmed by two independent pulmonologists, and a favorable clinical response was defined as a complete or partial recovery of symptoms and signs after one week of steroid treatment.

Results

Patients

There were 12 patients with a histopathological diagnosis of OP and concomitant diagnosis of a hematologic malignancy in our database from 1 January 2000 to 1 July 2020. Before OP onset, 7 patients accepted chemotherapy, including 1 patient who accepted SCT, 1 who received targeted therapy (e.g., rituximab) and 3 with ongoing infection. The other 5 patients had OP associated with hematologic malignancies, which were the primary pathologic process without any other related reasons. None of these 5 patients accepted chemotherapy, targeted therapy or SCT. There were 3 female patients, included one with myelodysplastic syndrome (MDS), one with acute myelogenous leukemia (AML, M5), and one with multiple myeloma (MM). One of the 2 male patients had aplastic anemia (AA), and the other T cell lymphoma (TCL). The patients' ages ranged from 43 to 67 years, and three of them had a smoking history (range from 30 to 80 pack-years).

Clinical Characteristics

The five cases of OP associated with hematologic malignancies presented symptoms similar to those of pulmonary infection, such as fever, cough and dyspnea (Table 1). One patient had a history of hemoptysis, which might have been caused by MDS-induced thrombocytopenia. Two of the patients had a history of productive cough with sputum, but all five patients were observed to have moist inspiratory rales. Consistent with the non-fibrosis on CT scan, none of the patients exhibited Velcro rales.

Table 1
Demographic and clinical characteristics of OP associated with hematologic malignancies

Patients NO.	Age(year)/Gender	Smoking history (pack-year)	Hematologic malignancies	Symptoms	Duration from onset to OP diagnosis	Lung biopsy	Respirator support	Admitted to ICU	Steroid treat hospital
1	52/F	0	Myelodysplastic syndrome (MDS)	Fever, cough, dyspnea, hemoptysis, chest pain	2 months	Bronchoscopic biopsy	High-flow nasal cannula oxygen therapy and noninvasive mechanical ventilation	3 weeks	methylpredni 40 mg/day (0.8 mg/kg/d intravenous infusion)
2	43/F	30	Acute myelogenous leukemia (AML, M5)	Fever, cough, dyspnea, fatigue, weakness,	1.5months	Bronchoscopic biopsy	High-flow nasal cannula oxygen therapy	2 weeks	methylpredni 40 mg/day (0.7 mg/kg/d intravenous infusion)
3	67/M	45	Aplastic anemia (AA)	Fever, cough, dyspnea, expectoration, chest pain	6 months	Bronchoscopic biopsy	Noninvasive mechanical ventilation	2 weeks	methylpredni 40 mg/day (0.7 mg/kg/d intravenous infusion)
4	57/M	80	T Cell Lymphoma (TCL)	Fever, cough, dyspnea, expectoration, chest pain	1 months	2 times of bronchoscopic biopsy, CT-guided percutaneous lung biopsy	Invasive mechanical ventilation	3 weeks	methylpredni 40 mg/day (0.7 mg/kg/d intravenous infusion)
5	68/F	0	Multiple myeloma (MM)	Fever, cough, dyspnea,	4 months	Bronchoscopic biopsy	High-flow nasal cannula oxygen therapy	1 week	methylpredni 40 mg/day (0.6 mg/kg/d intravenous infusion)

All five OP patients were hospitalized for diagnosis, and all were primarily diagnosed with pulmonary infection. Because of unfavorable responses to antibiotics and immune deficiency, pulmonary aspergillosis were the most frequently considered before the diagnosis of OP. All patients were found to have anemia, and four of them (excluding the patient with TCL) showed hypolymphocytosis in blood routine tests. Interestingly, after the use of steroids, all patients showed improvement of anemia without treatment for the hematologic malignancies. Before the diagnosis of OP, all patients accepted anti-infection treatments for more than 4 weeks, including piperacillin-tazobactam, ceftazidime-sulbactam, meropenem, and voriconazole. However, none of them received antiviral treatment, indicating that bacterial and fungal infections were the most considered differential diagnoses in OP associated with hematologic malignancies. Furthermore, all five OP patients were admitted to the intensive care unit (ICU) for respiratory failure (Table 1).

Radiologic findings

All patients underwent high-resolution computed tomography (HRCT) before OP diagnosis, and one of them even completed positron emission tomography-computed tomography (PET-CT). As in previous studies[10–12], there were patchy consolidative opacities and airspace consolidation along the bronchovascular bundle or in the subpleural area on HRCT (Fig. 1). However, some uncommonly described findings on HRCT were observed in these cases. One MDS case and one AML case were showing multiple nodules along the bronchovascular bundle with ground-glass opacity (GGO). The HRCT scan of the MDS case even showed a halo of GGO as a typical early sign of pulmonary fungal infection (Fig. 2A). Additionally, the AML case exhibited interlobular septal

thickening and a reticulonodular pattern (Fig. 2B). Interestingly, both cases progressed rapidly and developed extensive bilateral opacity on HRCT in less than two weeks (Fig. 2C, D).

PET-CT was conducted on the TCL patient, and showed a high standardized uptake value (SUV)_{max} of the lung and pleura (range from 2.5–3.5). On the other hand, PET-CT showed a higher SUV_{max} of the retroperitoneal and intraperitoneal lymph nodes (greater than 7.5), indicating that pulmonary lesion may be different from lymphadenopathy.

Diagnosis

Since OP is a rare disease and is defined by a special pathological pattern, it takes a long time to diagnose this condition[2]. The duration from onset to OP diagnosis was extensive, ranging from 1 to 6 months in the 5 OP cases. OP was frequently diagnosed by lung biopsy, including bronchoscopic and CT guide percutaneous biopsy. All 5 patients underwent bronchoscopic biopsy. Due to the subpleural lesion and limitation of the biopsy sample, a TCL patient failed to obtain a proper diagnosis for lung lesions even after 2 bronchoscopic biopsies. Finally, the OP diagnosis was confirmed in via CT guide percutaneous biopsy.

Cytological detection was conducted in BALF from the five patients, and no malignant cells were found. Four of them had differential cell counts and T cell subsets in BALF, except for the MM case. The ratios of lymphocyte ranged from 15–30%, and the ratios of the CD4+/CD8 + T cells ranged from 1.5 to 3.0. However, the neutrophil ratios were under 15% in all 4 cases. In addition, malignant cells were not observed in the alveolar space or wall from the biopsy sample.

Although bronchoscopy revealed purulent sputum in the TCL patient with OP, the pathogen-detection results were negative in sputum and BALF. Bronchoscopy of the other 4 patients revealed only a few secretions without edema and congestive mucosa in the airways. To detect possible pathogens, next-generation sequencing (NGS) technology was conducted in blood and BALF from the MDS and AML cases. The sequence analysis did not identify causative pathogens for the two cases.

Treatment And Outcome

Once the five patients were diagnosed with OP, all were treated with intravenous steroids (methylprednisolone, 40 mg/day) for more than 1 week. Fever and cough were the earliest and most frequently improved symptoms after steroid treatment. The five patients have underwent steroid (intravenous and oral) treatment for 3 to 6 months. During follow-up, we have found that the respiratory symptoms and radiological abnormalities were completely reversed after 1–3 months of steroid use (Table 1). One patient died due to AA at the 13th month of follow-up, and the other four patients survived during follow-up.

Due to agranulocytosis, the AML patient was treated with voriconazole and cefoperazone-sulbactam after OP diagnosis. The other four OP patients discontinued anti-fungus treatment after no evidence of fungal infection was found. Because of mild neutropenia, the AA and TCL patients received piperacillin-tazobactam treatment after their OP diagnosis.

Discussion

Since the etiology of OP was is multifactorial, OP with hematologic malignancies could be caused by anti-cancer drugs[13, 14], transplantation (SCT, BMT and CBT)[15, 16], immunodeficiency-induced infection and secondary CTD[2, 12, 17]. To exclude other drugs or disease-induced OP, we employed some traditional methods, such as antigen and antibodies of pathogens' detections, Gram stain and cultures. The new and promising NGS was also employed to detect pathogens. Finally, the authors summarized five OP patients underlying only hematologic malignancies, implying that hematologic malignancies might be a causative factor for OP.

The demographic data showed that the ages in our study ranged from 43 to 68 years, indicating that younger patients with hematologic malignancies might be less likely to develop OP[10]. Our results also showed an improvement of anemia following the reversed OP, indicating that the process of OP might aggravate anemia in hematological malignancies. All patients in our study were admitted to the ICU, and three of them underwent mechanical ventilation. A previous study reported that OP cases with multiple possible causes in other malignancies were also observed with a high ratio of severe cases[12]. However, OP with other benign causes was described with a favorable prognosis[2]. It is possible that OP associated with hematological malignancies is more likely to develop into a severe case than OP with benign underlying diseases, suggesting that physicians should exercise caution with OP in patient with hematological malignancies.

Previous studies[8, 10, 11] demonstrated that radiological findings were not distinctive, and authors also found patchy consolidative opacities and airspace consolidation along the bronchovascular bundle or in the subpleural region on HRCT. However, two patients in our case series and 7 OP patients in another study[18] were observed to exhibit multiple nodules along the bronchovascular bundle with GGO on HRCT, which were described as highly indicative of invasive pulmonary aspergillosis (IPA). As the disease progress, the two patients in our study developed extensive consolidation in one week, which confirmed that the radiological findings of OP with hematologic malignancies lacked a special pattern and could mimic some other diseases, such as IPA. Therefore, physicians can not excluded OP only by radiological findings in hematologic malignancy patients, especially in patients with a poor response to anti-infection treatment. Additionally, there is limited information on PET-CT findings in OP, and this paper provides PET-CT findings of OP associated with TCL. The SUV_{max} of the OP lesion was increased, but was still lower than that of the malignant lesion. This implied that OP and malignant or metastatic lesions could be distinguished through PET-CT.

This study found that the patients of OP with hematologic malignancies had similar symptoms to those of pulmonary infection (Table 2), with a long duration from the onset to the diagnosis of OP. Due to the lack of distinctive symptoms and examinations, it seems difficult to distinguish OP from infection. Therefore, bronchoscopic, CT-guided percutaneous and surgical lung biopsies were employed in the diagnosis of OP with hematologic malignancies (Table 2). At the beginning of the 21st century, surgical lung biopsy was more frequently used[18–20] (Table 2). However, in the last ten years, bronchoscopic and CT-guided percutaneous biopsies have been more frequently used[13, 21, 22]. Hematologic malignancies might lead to contraindications for surgery, such as severe thrombocytopenia and anemia. The 5 cases of OP associated with hematologic malignancies were confirmed through bronchoscopic and CT-guided biopsy, and all of these patients well tolerated the minimally invasive biopsy. This case series revealed that bronchoscopic and CT-guided percutaneous biopsy were safe and effective in the diagnosis of OP with hematologic malignancies. Because of the limited sample size and undiagnosed pathological pattern, the OP patient with underlying TCL in our study underwent bronchoscopic biopsy 2 times, and the diagnosis was confirmed through CT-guided percutaneous biopsy. It seems that CT-guided percutaneous biopsy might be more effective in subpleural lesions than bronchoscopic biopsy.

Table 2
Summary of previous reports on organizing pneumonia associated with hematologic malignancy.

Reference	OP cases	Primary malignancy	Preceding chemotherapy or radiotherapy	Radiologic findings	Lung biopsy	Treatment	Outcome
Mokhtari 2002 [12]	43 (16 with hematologic malignancy)	7 Lymphoma, 9 Leukemia	9 BMT	Varied; more likely infiltrates than nodules or masses	Surgical and bronchoscopic	Prednisone in 47% of total group	3 died within 1 month of OP diagnosis, 29 improved
Dai 2001 [23]	1	CML)	Allogenic BMT (5 months prior to OP onset)	NA	Surgical	NA	Died at 10 d postbiopsy
Kobara 2000 [7]	3	MDS	NA	GGO and air space consolidation	Bronchoscopic	Without treatment	2 improved, 1 relapsed in 6 months
White 2000 [19]	9 (63 underwent lung biopsy)	6 Lymphoma, 3 Leukemia	2 allogenic BMT, 1 auto BMT	Diffuse patchy infiltrates or multiple nodules	Surgical	Steroid	11 (18%) died at 30 d postbiopsy
Dunn 2001 [20]	3 (15 underwent lung biopsy)	Hematologic malignancy(not specific)	3 BMT	infiltrates	Surgical	Steroid	2 died within 17 days postbiopsy
Wohlrab 2001 [24]	1	Lymphoma	Chemotherapy (MOPP/ABV)	NA	Bronchoscopic	Steroid	Response to steroid, died of Pulmonary mucormycosis 2 years later
Kim 2002 [18]	7 (31 underwent lung biopsy, 13 pulmonary aspergillosis)	Hematologic malignancy(not specific)	NA	Highly indicative of invasive pulmonary aspergillosis, nodules or masses with a halo sign, segmental area of consolidation with ground-glass attenuation and centrilobular nodules	Surgical	NA	NA
Karamlou 2004 [25]	1	MDS	NA	Nodules in a bronchocentric distribution	Surgical	Steroid and cyclophosphamide	Response to cyclophosphamide
Garg 2006 [26]	1	MDS	NA	Left lower lobe infiltrate with pleural effusion	Bronchoscopic	Steroids	Improved
Daniels 2007 [17]	6	3 lymphoma, 2 leukemia, 1 MDS	4 chemotherapy, 2 radiotherapy, 2 BMT, 1 allogenic SCT	Patchy consolidation or diffuse parenchymal infiltrates	4 surgical, 2 bronchoscopic	5 steroid, 1 without treatment	Improved, 4 died of hematologic malignancy within 19 months
Tomonari 2007 [16]	4	1 AML, 1 ALL, 2 MDS,	4 CBT	Diffuse GGO, patchy consolidation, air bronchograms	Bronchoscopic	Steroid	Improved
Kamiya 2008 [27]	1	MDS	NA	Bilateral infiltrates	Bronchoscopic	Steroid	Response to steroid, died of disseminated cryptococcosis
Tanaka 2011 [28]	1	NA	SCT	GGO and bilateral consolidation, air bronchograms	Surgical	NA	NA
Asano 2014 [21]	1	MDS	Chemotherapy	Pulmonary bilateral infiltrates	Bronchoscopic	Steroid, allogenic SCT	Resistant to steroid, improved after SCT
Alnimer 2016 [14]	1	MDS	Azacitidine	Patchy consolidation, GGO and pulmonary interstitial thickening	CT-guided percutaneous lung biopsy	Steroid	Partly improved
Tzelepis 2016 [29]	1	Lymphoma and MDS	Chemotherapy	Bilateral consolidations	Surgical	Steroid	Improved, died of sepsis within 7 months

SCT (stem cell transplantation), CML (chronic myelogenous leukemia), MOPP/ABV (nitrogen mustard, vincristine, procarbazine, prednisone, doxorubicin, vinblastine, bleomycin), MDS (myelodysplastic syndrome), CBT (cord blood transplantation), sPAP (secondary pulmonary alveolar proteinosis), PV (polycythemia vera)

Reference	OP cases	Primary malignancy	Preceding chemotherapy or radiotherapy	Radiologic findings	Lung biopsy	Treatment	Outcome
Vieira 2018 [22]	67 (7 with hematological malignancies)	5 leukemia, 2 lymphoma in two	NA	Consolidation	54 underwent CT-guided percutaneous lung biopsy	79.1% accepted steroid treatment	96.2% improved
Inoue 2019 [6]	1 (clinical diagnosis)	MDS	NA	Bilateral patchy consolidations with reversed halo sign	Bronchoscopic, insufficient specimen for pathological diagnosis.	Steroid	Improved, relapsed with sPAP, died at 8 months postbiopsy
SCT (stem cell transplantation), CML (chronic myelogenous leukemia), MOPP/ABV (nitrogen mustard, vincristine, procarbazine, prednisone, doxorubicin, vinblastine, bleomycin), MDS (myelodysplastic syndrome), CBT (cord blood transplantation), sPAP (secondary pulmonary alveolar proteinosis), PV (polycythemia vera)							

As described in a previous study [2], steroid treatment led to a favorable outcome in this case series. To discuss steroid treatment in OP associated with hematologic malignancies, the authors searched OP and hematologic malignancies in PubMed (Table 2). Most of these papers used steroids to treat OP with a favorable response. However, some other studies found that OP with hematological malignancies could be steroid resistant and improved with SCT[21] or without treatment[7]. The follow-up brought unfavorable clinical outcomes for the non-steroid treatment. One of the OP cases without treatment relapsed in 6 months, and another case progressed[7], indicating that observation without treatment might not be suitable for the management of OP with hematologic malignancies. Furthermore, our study excluded the other possible causative factors, such as infection, which could progress after steroid treatment. For the above reasons, the authors suggest that steroids might be the first-line drug treatment for OP associated with hematologic malignancies.

Conclusion

Collectively, our findings support that hematologic malignancies might be a causative factor for OP and that biopsy may be an effective and safe method to confirm the diagnosis. Although OP associated with hematologic malignancies might more frequently develop into severe cases, the OP lesions seem to be steroid-responsive with favorable outcomes during follow-up.

Declarations

Ethics approval and consent to participate

The study was approved and supervised by the Medical Research Ethics Committee of the Second Xiangya Hospital, Central South University. Informed consent was waived. This research has been performed in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable

Availability of data and material

The datasets or analyzed during the current study are not publicly available due that they are privacy of the patients, but are available from the corresponding author on reasonable request.

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Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Huihui Zeng performed part of the analyses and drafted the manuscript. Xiaoqing Shen contributed to a part of analyses and most of the search work. Xue He and Shan Cai contributed to a part of analyses and helped to draft the manuscript. Ping Chen and Yan Chen contributed to a part of the research design. Hong Luo is the co-principal investigator of the study, and she supervised the study and helped to draft the manuscript. Every author contributed to reviewing the paper.

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None.

Disclosure Statement

The authors declare that they have no conflicts of interest.

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Figures

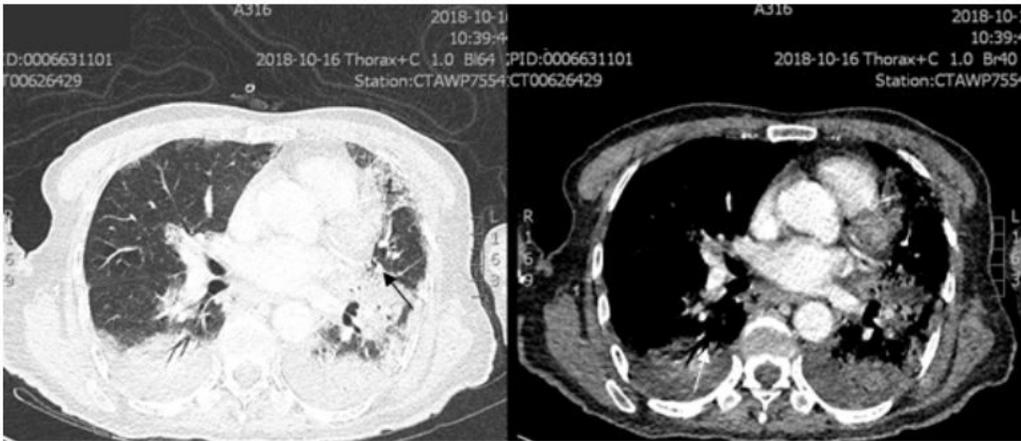


Figure 1

The common findings of OP associated with hematological malignances on HRCT There were patchy consolidative opacities and airspace consolidation along the bronchovascular bundle or in the subpleural on HRCT.



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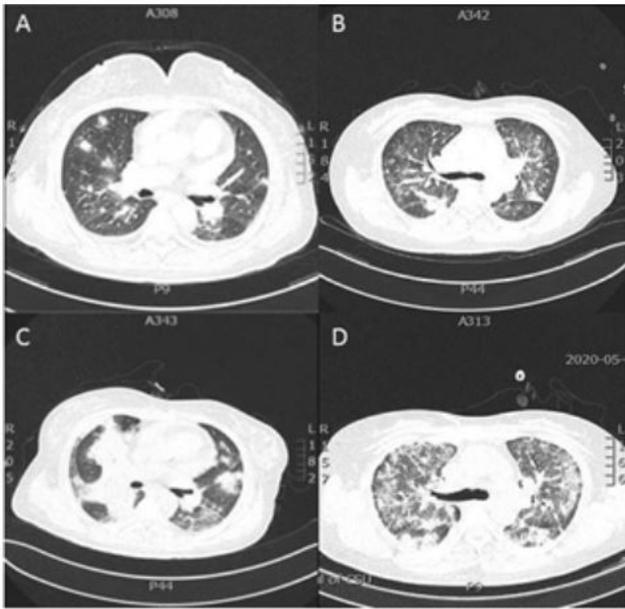


Figure 2

HRCT of OP associated with hematological malignances mimics IPA A: The HRCT scan of MDS case even showed a halo of GGO as typical early sign of pulmonary fungal infection. B: the AML case was also observed with GGO, interlobular septal thickening and reticulonodular pattern. C and D: progressed rapidly to extensive bilateral opacity on HRCT in less than two weeks from A and B respectively.

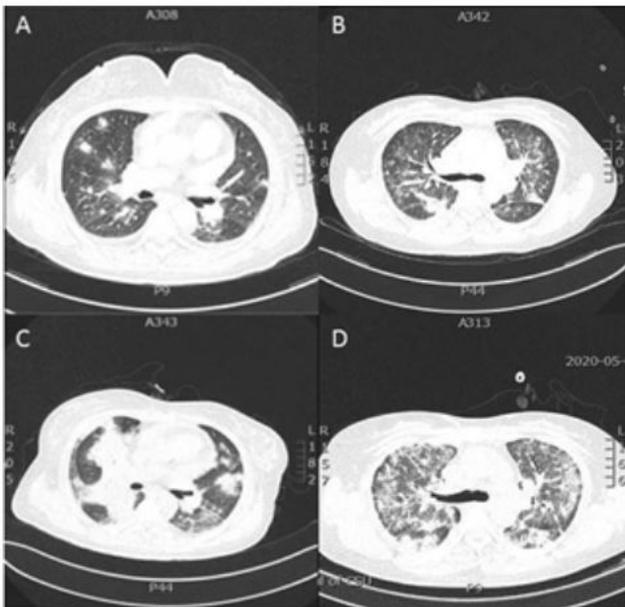


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