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Non-infectious respiratory complications after allogeneic bone marrow transplantation: single center experience in Egypt

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Abstract

Background Hematopoietic progenitor cells are infused intravenously, known as hematopoietic stem cell transplantation. The range of pulmonary problems after transplantation of hematopoietic stem cells varies significantly from infectious to non-infectious aetiologies.

Objectives To study noninfectious respiratory complications in patients subjected to allogeneic bone marrow transplants.

Patients and methods This retrospective study was carried out on 1000 patients with hematopoietic stem-cell transplantations. These patients were presented with respiratory symptoms suggestive of pulmonary complications following bone marrow transplant.

Result The number of patients in this period was 1000 patients, and 247 of them had non-infectious pulmonary complications. Number and percent of bronchiolitis obliterans, diffuse alveolar hemorrhage, graft-versus-host disease (GVHD), pulmonary edema, Bronchiolitis obliterans with GVHD, Chemotherapy pneumonitis, Idiopathic pneumonia syndrome and Thoracic air leak syndrome to all number of cases were twenty-five (2.5%), sixteen (1.6%), eighty-one (8.1) sixty-four (25.9%), nineteen (1.9%), twenty-one (2.1%), thirteen (1.3%) and eight (0.8%) respectively, but number and percent of bronchiolitis obliterans, diffuse alveolar hemorrhage, GVHD, pulmonary edema, bronchiolitis obliterans with GVHD, chemotherapy-associated pneumonitis, Idiopathic pneumonia syndrome, and thoracic air leak syndrome to all complicated cases only were twenty-five (10.1%), sixteen (6.5%), eighty-one (32.8%), sixty-four (25.9 %), nineteen (7.7%), twenty-one (8.5 %), thirteen (5.3 %) and eight (3.2%) respectively.

Conclusions Noninfectious respiratory complications included GVHD, pulmonary edema, bronchiolitis obliterans and diffuse alveolar hemorrhage bronchiolitis obliterans with GVHD, chemotherapy-associated pneumonitis, Idiopathic pneumonia syndrome, and thoracic air leak syndrome. Some of them occurred early, and some occurred late. The incidence of non-infectious respiratory complications is affected by increased patient age and female gender.

Keywords Hematopoietic stem cell transplantation, Noninfectious, Respiratory complication

Background

Following chemotherapy and radiation treatment, an individual may undergo hematopoietic stem-cell transplantations (HSCT), which administer intravenous hematopoietic progenitor cells to restore marrow function [1]. Multiple myeloma, Hodgkin and non-Hodgkin lymphomas, acute and chronic leukemia, as well as non-malignant conditions such as aplastic anemia and

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congenital immuno-deficiency syndromes, all are treated with HSCT [2].

The patient (autologous), a sibling or unrelated individual (allogeneic), or an identical twin (syngeneic) may serve as the donor source [3]. Following HSCT, engraftment involves the restoration of the neutrophil and platelet counts, which normally occurs three weeks later [4]. With the prudent use of broad-spectrum antibiotic prophylaxis, the range of pulmonary problems after hematopoietic stem cells has shifted increasingly from infectious to non-infectious aetiologies in recent years [5, 6]. The frequency of infection complications following HSCT has reduced because of improvements in the preventative regimen. The importance of non-infectious complications has increased because the frequency of non-infectious consequences has remained constant [7, 8].

The non-infectious respiratory complications following HSCT, including diffuse alveolar hemorrhage and idiopathic pneumonia syndrome, chronic progressive small airways disease, including bronchiolitis-obliterans syndrome, [8] and vascular problems such as pulmonary veno-occlusive diseases and cytolytic thrombosis [7].

Graft versus host disease is a common complication of allogeneic bone marrow transplants. It attacks the new bone marrow cells against the receiver's organs [9].

The purpose of this work is to determine non-infectious respiratory complications based on the onset of the disease into the peri engraftment period (0-30), early posttransplantation (31-100), late post-transplant (after 100 days) in patients subjected to allogeneic bone marrow transplant.

Patients and methods

The retrospective cohort study was conducted from 2009 to 2019 at Nasser Institute and Tanta University Chest Hospital. The inclusion criteria included patients above 18 years who underwent allogeneic bone marrow transplants.

Those individuals come with respiratory symptoms suggestive of pulmonary complications after a bone marrow transplant. The local ethics committee of our center has approved the research protocol number (33468). Patients were followed for 6 months at Nasser Institute. All the studied patients received prophylactic antibiotics, antifungal, and antiviral as a part of the protocol. 1000 patients were examined, and 247 of them had non-infectious complications. The exclusion criteria were patients with incomplete data.

The data related to HSCT were collected from paper-based medical records.

Data included: history taking, baseline investigations included: [complete-blood-count, aspiration of bone-marrow, biopsy from bone-marrow, tests for the functioning of the liver, such as (ALT and AST), renal function tests including (bilirubin, urea and creatinine), electrolytes including (Na, Ca, K and alkaline phosphatase), fasting and post prandial glucose level, blood Group, R.H. and HLA typing, virology including (HBV, HCV, HIV, Toxoplasma virus, cytomegalo virus), electro cardiograph, echocardiography, chest X ray: postero anterior view, abdominal and pelvic ultra sounography.], diagnosis, chest conditions, comorbidity (D.M., HTN, renal disease, hepatic disease, cardiac disease), a drug used and radiotherapy (dose, type)

Diagnosis: criteria of diagnosis of some common non-infectious pulmonary complications:

Pulmonary edema

Clinical: Standard clinical indicators among individuals with dyspnea include gaining weight, bilateral lung rales, and hypoxemia.

Radiological: Bilateral interstitial infiltration, mainly peri-hilar, either with or without pleural effusion, is among the anomalies seen on chest radiographs [3].

Diffuse alveolar hemorrhage (DAH)

Clinical: fast onset of hypoxemia, nonproductive coughing, fever, and dyspnea; hemoptysis is uncommon.

Radiological: Typically, the infiltrations are bilaterally and mostly central [10].

Graft versus host disease

Clinical: Dyspnea, nonproductive coughing, crepitations, and chest wheezing are all respiratory manifestations and warning indications.

Radiological: Focal or diffused infiltration has been identified on HRCT and chest imaging.

PFT

A decline in vital capacity and forced expiratory volume in the initial second, followed by a sharp decline in the forced expiratory volume in the initial second/vital capacity ratios, indicative of airway obstruction, are shown during pulmonary function testing [9].

Bronchiolitis obliterans

Clinical: increasing dyspnea with a cough that is dry and wheezing upon expiration.

Radiological: Radiology of the chest reveals hyperinflation. On an expiratory scan, C.T. scans may reveal trapped air and a mosaic pattern.

Pulmonary function tests (PFT) indicated air flow restriction. Normal lung volumes reduced, forced expiratory volume in the initial second, and reduced forced volume capacity are the norms for diffusing capacity.

Clinical signs, anomalies in the HRCT, and abnormal PFT results are used to make the diagnosis of B.O. [11].

Chemotherapy-associated pneumonitis

Clinical: nonproductive cough and increasing dyspnea.

Radiological; bilateral interstitial infiltrates [12].

Idiopathic pneumonia syndrome (IPS) Clinical**:** dyspnea, hypoxemia, nonproductive coughing.

Radiological: non-lobar radiograph infiltrations [13].

Thoracic air leak

Clinical: acute chest pain and dyspnea

Radiological: On a C.T. scan, the air in the mediastinum, pleural space, and sub-cutaneous tissues are all clearly visible [3].

The most probable etiology of respiratory complication (original disease, therapy, transplant).

Statistical analysis

Statistical analysis was done by SPSS v26 (IBM Inc., Chicago, IL, USA). Quantitative variables were presented as mean and standard deviation (S.D.). Qualitative variables were presented as frequency and percentage (%).

Result

The number of patients in this period with non-infectious complications was 247(24.7%); the mean values of age in years were (28.92 ± 9.02) 156 were male, while 91 were female. Regarding smoking status, 215 nonsmokers, 30 were ex-smokers, and 2 were smokers. Regarding comorbidities, 236 had no comorbidities, 6 were asthmatic, 2 had D.M., and 3 had HTN. 19% were transplanted due to aplastic anemia, 2.4% were transplanted due to B thalassemia major, 2.4%were transplanted due to Fanconi anemia, 61.1 %were transplanted due to leukemia, 7.3% were transplanted due to lymphoma, 6.1 % were transplanted due to myelodysplastic syndrome, 0.8due to myelofibrosis and 0.8 due to Paroxysmal nocturnal hemoglobinuria Table 1.

There were 39.3% survived and 60.7% died. 78.1% didn't need mechanical ventilation and 21.9 % needed mechanical ventilation Table 2.

The number and percentage of bronchiolitis obliterans, diffuse alveolar hemorrhage, graft versus host disease (GVHD), pulmonary edema, and patients with both bronchiolitis obliterans and GVHD in relation to cases with non-infectious complications were 10.1%, 6.5%, 41.3%, 34.4%, and 7.7% respectively Table 3.

There was a significant increase in age in patients with GVHD, but there was a significant decrease in patients with pulmonary edema. There was an insignificant difference in sex in patients with different non-infectious respiratory complications. All cases of diffuse alveolar hemorrhage and pulmonary edema occurred early, while all cases of bronchiolitis obliterans occurred late, but 27.3% of GVHD occurred early, and 72.7% occurred late. Also, for cases with bronchiolitis obliterans and GVHD, 33% occurred early, 67% occurred late chemotherapy chemotherapy-associated pneumonitis, 80.95% occurred early, and 19.05% occurred late. In idiopathic pneumonia syndrome, 69.23% occurred early, and 30.77% occurred late; in thoracic air leak syndrome, 25.00% occurred early, and 75.00% occurred late. There was a significant increase in mortality in patients with GVHD, followed by

Table 1 Characteristics of patients with non-infectious complications in the stud

	(*N*=247)
Age	18 – 58 (28.92 ± 9.02)
Sex	
Female	156 (63.2%)
Male	91(36.8%)
Smoking status	
Nonsmoker	215(87.0%)
Ex smoker	30 (12.1%)
Smoker	2 (0.8%)
Comorbidities	
No	236 (95.5%)
Asthmatic	6(2.4%)
D.M.	2 (0.8%)
HTN	3(1.2 %)
Indications of transplant	
Aplastic anemia	47(19%)
B thalassemia major	6(2.4%)
Fanconi anemia	6(2.4%)
Leukemia	151(61.1%)
Lymphoma	18(7.3%)
Myelodysplastic syndrome	15(6.1%)
Myelofibrosis	2(0.8%)
Paroxysmal nocturnal hemoglobinuria	2(0.8%)

Data are presented as mean ± S.D or number (%). DM: diabetes mellitus. HTN: hypertension

Table 2 Prognosis of patients complicated with non-infectious complication

	N (%)
Mortality	
Survive	97 (39.3%)
Died	150 (60.7%)
Mechanical ventilation	
No need	193(78.1%)
Need	54(21.9%)

Data are presented as number (%)

Table 3 Number and percentage of each complication in relation to cases with non-infectious complications and in relation to all cases

Non-infectious Complications	N	% To non-infectious cases	% To all cases
Bronchiolitis obliterans	25	10.1	2.5
Diffuse alveolar hemorrhage	16	6.5	1.6
GVHD	81	32.8	8.1
Pulmonary edema	64	25.9	6.4
Bronchiolitis obliterans and GVHD	19	7.7	1.9
Chemotherapy associated pneumonitis	21	8.5	2.1
Idiopathic pneumonia syndrome	13	5.3	1.3
Thoracic air leak syndrome	8	3.2	0.8
Total	247	100	100

Data are presented as number (%). GVHD: graft-versus-host disease

patients with both bronchiolitis obliterans and GVHD. Bronchiolitis obliterans patients, then pulmonary edema patients, then patients with diffuse alveolar hemorrhage, then idiopathic pneumonia syndrome, then chemotherapy-associated pneumonitis, and the lowest mortality was in patients with thoracic air leak syndrome Table 4.

Discussion

In the present study, as regards the number of cases 247 were complicated with non-infectious respiratory complications.

In contrast, this incidence was much higher than Onizuka et al. [14], identifying 535 patients with non-infectious pulmonary complications among 13,573 individuals (3.9%), according to data from 2001 to 2009 from the Japan Transplant registry. At 100 days, a year, and three years following HSCT, this cohort's cumulative frequency of non-infectious pulmonary problems was 2.1%, 3.7%, and 4.1%, respectively. The higher incidence in our study may be as it is single center experience.

In the present study, the mean value of age was range (18 – 58) and the mean (was 28.92 ± 9.02) Onizuka et al. [14] found that high recipient age was significantly correlated with a raised risk of non-infectious pulmonary complications.

While Patriarca et al. [15] observed an insignificant difference according to age among individuals with and without late-onset non-infectious respiratory issues.

In the present study, the frequency of non-infectious respiratory complications was higher in females than in males.

Bergeron et al. [16] agreed with the present study and reported that female was significantly associated with non-infectious respiratory issues compared to males. In contrast, Patriarca et al. [15] observed that males represented most individuals with noninfectious respiratory complications.

In the current study, the incidence of nonsmokers was higher than smokers.

This result, agreed with Ho et al. [17], showed that smoking is not associated with the development of severe pulmonary complications.

In the present study, the indication of bone marrow transplant in a patient with non-infectious complications

Table 4 Statistical analysis of age, sex, early or late and mortality of each complication

	Age	Sex		Early %	Late%	Mortality N (%)
		Male%	Female %			
Bronchiolitis obliterans	40.5 ± 13.35	28%	72%	0%	100%	11 (44%)
Diffuse alveolar hemorrhage	35.06±10.90	37.5%	62.5%	100%	0%	27 (42.19%)
GVHD	42.03±10.11	40.5%	59.5%	27.3%	72.7%	57 (70.37%)
Pulmonary edema	32.78±10.39	34.1%	65.9%	100%	0%	28 (43.75%)
Bronchiolitis obliterans and GVHD	40.02±10.08	39 %	61 %	33 %	67%	13 (68.42%)
Chemotherapy associated pneumonitis	34.1 ± 15.28	47.62%	52.38%	80.95%	19.05%	7 (33.33%)
Idiopathic pneumonia syndrome	38.64±11.68	61.54%	38.46%	69.23%	30.77%	5 (38.46%)
Thoracic air leak syndrome	36.6 ± 13.61	62.50%	37.50%	25.00%	75.00%	2 (25%)

Data are presented as mean ± S.D or number (%). GVHD: graft-versus-host disease

was 61.1% leukemia, 7.3% lymphoma, 19% aplastic anemia, 2.4% Fanconi anemia, 6.1% myelodysplastic syndrome, 0.8% paroxysmal nocturnal hemoglobinuria, 0.8% myelofibrosis and 2.4 % in B thalassemia major.

In agreement with this study, Ueda et al. [18] reported insignificant differences among individuals with and without noninfectious respiratory complications regarding the indication of stem cell transplantation.

In the current work, the number of people who survived was 97 (39.3 %), while the number of those who died was 150 (60.7%), mainly of those complicated with late-onset noninfectious pulmonary complications; this may be due to the presence of cGVHD.

In agreement with the present study, Bergeron et al. [16] stated that the occurrence of late-onset noninfectious pulmonary complications was associated with an increased hazard of death. In contrast to this result, Sakaida et al. [19] reported a non-significant difference in mortality among individuals with and without late-onset noninfectious respiratory complications. A smaller sample size is a suitable explanation for this difference.

In the present study, patients who didn't need mechanical ventilation were 193 (78.1%) while those need mechanical ventilation were 54 (21.9%)

Sadon et al. [20] considered that Higher morbidity and death rates and poor outcomes were predicted by mechanical ventilation.

In our study, all cases of pulmonary edema and diffuse alveolar hemorrhage occurred early, while all cases of bronchiolitis obliterans occurred late, but 77.9 % of GVHD occurred late, and 24.6% occurred early. The occurrence of bronchiolitis obliterans was late mainly because it was a complication of GVHD. This agreed with many studies that revealed that bronchiolitis obliterans syndrome is now recognized as the majority of late-onset noninfectious respiratory complications. Filipovich et al. [21], Jagasia et al. [22], Shulman et al. [23]. In agreement with this study, Patel et al. [24] showed that with a median time to start of 50 days after an allogeneic transplant of stem cells, diffuse alveolar hemorrhage was more inclined to emerge sooner in the posttransplantation course.

In the current research, participants with graft versus host diseases and bronchiolitis obliterans had a substantial age rise. In agreement with the present study, Yoshihara et al. [25] found that potential risk factors for developing bronchiolitis obliterans included older recipients and donor age.

In the present study, thoracic air leak syndrome occurred late and mainly in males (62.5%); the mean age was (36.6±13.61).

In agreement with this study, Sakai R. et al. [26] found late onset of air leak syndrome and male predominance. In contrast to this result, Moon, M.H. et al. [27] found more females with air leak syndrome than males.

Limitations

It was a single-center study, and the results may differ elsewhere. The retrospective nature of the study is insufficient to establish a causal relationship. This study was done on allogeneic patients, which may affect the results. There was little information on therapy management because most of these treatments are currently being studied and tested, so there's no official guide to treat these complications.

Conclusion

Noninfectious respiratory complications included GVHD, pulmonary edema, bronchiolitis obliterans and diffuse alveolar hemorrhage bronchiolitis obliterans with GVHD, chemotherapy-associated pneumonitis, Idiopathic pneumonia syndrome, and thoracic air leak syndrome. Some of them occurred early, and some occurred late. The incidence of non-infectious respiratory complications is affected by the increase in the patient's age and the increase in the female gender.

Abbreviations

GVHD	Graft versus host disease
HSCT	Haematopoietic stem-cell transplantations
ALT	Alanine transaminase
AST	Aspartate aminotransferase
R.H.	Rhesus
HLA	Human leukocyte antigens
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
DM	diabetes mellitus
HTN	Hypertension
DAH	Diffuse alveolar hemorrhage
CT	Computed tomography
PFT	Pulmonary function tests
IPS	Idiopathic pneumonia syndrome

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Authors' contributions

Study concept and design: M. M., and M. S.; analysis and interpretation of data: S. G., and B. E.; drafting of the manuscript: M. M.; critical revision of the manuscript for important intellectual content: B. E., and S. G.; statistical analysis: M. M.

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Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The local ethics committee of our center has approved the research protocol number (33468).

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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