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Editorial

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Biomarkers for Diagnosis and Treatment of Chronic Obstructive Pulmonary Disease (COPD): What is the Role of microRNAs?

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Chronic Obstructive Pulmonary Disease (COPD) is a heterogeneous respiratory disease characterized by a progressive, not fully reversible airflow limitation associated with an abnormal inflammatory response of the lungs to noxious stimuli.[1,2] Demographic data show that more than 200 million patients worldwide suffer COPD, leading the scientific community to speculate that in 2020 it will be the third important cause of mortality in the world.[3] Several immune system cells (e.g. macrophages, eosinophils) and biochemical mediators (e.g. tumor necrosis factor-alpha, transforming growth factor beta, Interleukins and metalloproteases) are involved in its development and in symptoms severity.[2] It has been suggested that in COPD patients there is a spill over of peripheral lungs inflammation markers into systemic circulation that in turns result in an increased level of different inflammatory markers such as: IL-1β, IL-6, IL-8, and TNF-α. The increase of those systemic inflammatory markers could be the link of COPD patients co-morbidities, since they are responsible *per se* of many other complication such as cardiovascular disease, hypertension, skeletal muscle weakness, diabetes, obesity and metabolic syndrome.[4] COPD diagnosis is based on clinical evaluation and spirometry and actually several biochemical parameters (i.e. interleukins, C-reactive protein (CRP), serum amyloid A, and fibrinogen) are increased in blood circulation during COPD exacerbations as well asduring COPD treatments.[5-7] COPD exacerbation and progression, is due to the absence of a plasmatic markers able to identify the stage of the disease and/or the response to the treatment. This represents, in real life, a common problem during COPD treatment that is also linked with an increase of sanitary health costs. Last year, the European Health Bill for COPD treatment increased by 10 million USD and the market is thought to increase up to 37.7 million USD by 2030.[8] Therefore, considering all these aspects the identification of biomarkers indicative for early diagnosis of COPD is mandatory. Recently we suggested that the search for phenotype-specific biomarkers could help to better understand the individual driving mechanisms of disease as well as identify drug targets possibly useful for personalized treatments of COPD.[7,9]

It has been suggested that systemic inflammatory markers levels (in plasma) such as Tumor Necrosis Factor-alpha (TNFα), Interleukin 6 (IL-6) and C-reactive protein (CRP), persist also in the stable period COPD patients and CRP levels correlate with the COPD Assessment Test.[10] On the other hand, CRP is not a specific marker of lung disease, while to date more appropriate marker could be represented by microRNAs (miRs), a class of gene expression regulators, that plays a role in the fine-tuning regulatory networks that govern inflammation and epithelial-to-mesenchymal transition tissue change.[11,12] Post-transcriptional control of gene expression is critical for the proper control of inflammation. There is now increasing evidence that miRNAs regulate inflammation and fibrosis in multiple organs including the lungs. A number of miRNAs such as miR-29b, miR-483-5p, miR-152, miR-629, miR-26b, miR-101, miR-

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133b, miR-532-5p and particularly miR-106b are significantly down regulated in plasma of COPD patients, while others such as miR-1343, miR-21 and miR-29 families, are emerging as common regulators of fibrosis.[13-15] It is worth to mention that microRNAs (miRs) represent an important mechanism for post-transcriptional control. There is a large body of work demonstrating the complex role that miRs play in the fine-tuning of the regulatory networks that govern inflammation and epithelial-to-mesenchymal transition tissue change (fibrosis).[11,12,15]

However, clinical research is necessary to validate the role of miRs in COPD; but it is important to consider that the identification of a miRs signature must be performed through a robust and sensitive technology able to identify a COPD diagnostic prediction testable to perform both, early diagnosis and monitoring of therapy.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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Editorial

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Alveolar Type I Epithelial Cells: The Forgotten Cells in Fetal Lung Development and Lung Injury

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The alveolar surface of the lung is covered by large flat type I epithelial cells. Even though type I cells represent only around 10% of the cells present in the alveolus; they cover much of the surface area in the developed lung.[1] Given their thinness and proximity to the capillary endothelium; it is well accepted that type I cells play an important role in gas exchange.[2] In addition, these cells are important to maintain adequate fluid balance in the alveolus[3] *via* the tight junctions,[4] ion transport channels[5] and aquaporin-5.[6] Recent studies also indicate that type I cells participate in innate immunity; they express toll-like receptor 4 and produce pro-inflammatory cytokines.[7,8] Studies from T1α knockout mice indicate that alveolar type I cells may be critical for normal lung development. T1α, a lung type I cell differentiation gene, is developmentally regulated and expressed only in type I cells. T1α knockout mice died at birth of respiratory failure. Histologic analysis show fewer alveolar type I cells and decreased alveoli.[9] All together, these investigations suggest a critical role for type I cells in gas exchange, alveolar fluid hemostasis, immunity and fetal lung development.

The typical flat morphology of type I cells begin to appear in the late canalicular period and increase in number during the saccular and alveolar stages of lung development.[10] It has been believed that type I cells are derived from type II cells.[11,12] However, recent studies[13] using specific markers for type I (T1alpha (T1α) and Receptor for Advanced Glycation Endproducts (RAGE))) and type II cells (SP-C, NKX2-1, and ABCA3) have demonstrated the presence in the distal lung of alveolar progenitor cells containing both phenotypes, before they became differentiated type I or type II cells. Therefore, these studies show that during fetal lung development, alveolar type I and type II epithelial cells are derived from a bipotent progenitor cell.[13] Hooper's group found that the numbers of "intermediate cells" expressing both phenotypes were strongly influenced by the degree of lung expansion,[14] supporting the role of mechanical signals in fetal lung development and differentiation of alveolar epithelial cells.

Many premature infants born with underdeveloped lungs develop Bronchopulmonary dysplasia (BPD), a chronic inflammatory lung disease with serious short- and long-term complications. Although the etiology of BPD is multifactorial, mechanical ventilation plays a central role.[15] Excessive stretch of the lung by mechanical ventilation can disrupt the integrity of the alveolar-capillary barrier, resulting in interstitial and alveolar edema. Neutrophils and macrophages recruited to the lung can then trigger and amplify an injury response by releasing cytokines and other inflammatory mediators.[16,17] Many of these pro-inflammatory cytokines are secreted by alveolar macrophages, fibroblasts, type II pneumocytes, and endothelial cells.[18] Distal lung parenchyma cells can be directly exposed to overstretch, and therefore to injury secondary to mechanical ventilation. It has been shown for example that type II epithelial cells release proinflammatory cytokines in response to mechanical injury.[19-22] Given that type I epithelial cells cover much of the distal epithelium of the lung, these cells are also at risk for injury mediated by mechanical ventilation. However, the contribution of type I cells to the pathogenesis of BPD is not clearly defined, in part because of the difficulty in isolating type I cells *in vitro*.[23] Nevertheless, recent studies have found these cells produce Tumor Necrosis Factor-alpha (TNF-α), Interleukin-1 beta or IL-1beta (IL-1β), and Interleukin 6 (IL-6) after exposure to Lipopolysaccharide (LPS).[24] In fact, some authors believe that alveolar type I epithelial cells

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are a more important source of pro-inflammatory cytokines than type II cells.[25] Moreover, the Receptor for advanced glycation end-products (RAGE) is found only on type I cells in the lung.[26] RAGE signaling is mediated *via* NF-κB pathway, stimulating production of pro-inflammatory cytokines and inducing apoptosis.[27]

The epithelial barrier is composed of tight junctions connected to the actin cytoskeleton *via* occludin or zonula occludens. It has been shown that mechanical strain of alveolar epithelial cells, mimicking mechanical ventilation with high tidal volumes, resulted in actin-mediated cell contraction with subsequent increased in paracellular permeability[28] and breakdown of intercellular junctions.[29,30] These junctions could be affected by mechanical injury, leading to pulmonary edema.[31,32] In addition to maintaining the integrity of the epithelial barrier by the tight junctions, epithelial cells need mechanisms to reabsorb the fluids present in the interstitium and alveolar spaces after lung injury mediated by mechanical ventilation.[33] This process is mediated by active transport of Na^+ through amiloride-sensitive cation channels Epithelial Na^+ Channels (ENaC) present in the apical cell membranes and the Na^+/K^+-ATPases localized mainly in the basolateral cell membrane.[34-37] Electron microscope studies provided clear evidence for the major abnormalities in the blood-gas barrier during lung injury. Damage of alveolar type I epithelial cells was observed in rabbits ventilated with a peak inspiratory pressure of 20 cm H_2O for 6 hours.[38] In these studies, some endothelial cells were detached from their basement membrane, resulting in the formation of intra-capillary blebs. There were also occasional breaks in endothelial cells. More prolonged exposure to injurious stress produced alveolar epithelial pathology ranging from inter- and intra-cellular gap formations with denuded basement membranes to extensive cell destruction.[39]

In summary, and as discussed in an excellent review by Dr. Rozycki,[23] alveolar development requires an orchestrated signaling cross-talk among different cells of the distal lung.[40] Given that type I epithelial cells are critical for normal lung development and to maintain the hemostasis of the distal lung, damage of these cells and/or their progenitors by mechanical ventilation and hyperoxia could not only disrupt normal pulmonary development but also have a significant contribution to the pulmonary edema and inflammation observed in patients with BPD. Future studies will provide more insights into the role of these forgotten cells in fetal lung development and lung injury of premature lungs.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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Research

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PM_{10} Emitted from Gravel Crushers and their Effects on Complete Blood Counts for Workers, Middle Governorate – Gaza, Palestine

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ABSTRACT

Case-control study was conducted during the period from April to August, 2013 on all gravel crushers at Middle Gaza Governorates. There were 87 individuals participants involved in this study, out of which 40 were case (exposed) and 47 control (non-exposed) groups respectively. PM_{10} (Particulate matter with an aerodynamic diameter of 10 micrometer or less) concentration level was measured in the six crushers, and all participants were subjected to Complete Blood Counts (CBC). This was conducted to evaluate the level of PM_{10} air pollution in crusher's plants, and their impacts on complete blood counts (CBC) for crushers workers. Results showed that an average of particulate matter contributions is 15153 µg/m^3 (microgram/cubicmeter), which is about 100 times higher than PM_{10} existing standard of 150 µg/m^3. As well as, it showed clear links between PM_{10} exposure and CBC changes among exposed group. Increasing in white blood cells count were more common among the exposed group, whereas in the non-exposed group, CBC did not change. Therefore, we can conclude that PM_{10} concentration level in crushers plants were much higher than the existing standard. Occupational exposure to PM_{10} leads to CBC changes especially increasing in white blood cells count.

KEYWORDS: PM_{10}; Complete Blood Count (CBC); Crushers; WBCs; HGB; RBCs; Gaza; Palestine.

ABBREVIATIONS: CBC: Complete Blood Count; WHO: World Health Organization; FBC: Full Blood Count; PM: Particulate Matter.

BACKGROUND AND INTRODUCTION

Many studies have shown that acute exposure to PM_{10} is associated with leukocytosis (increasing white blood cells count). Studies have observed that long-term PM_{10} exposures are associated with CBC changes such as increasing white blood cells count.[1-4]

In 2007, the World Health Organization (WHO) released data on estimated deaths worldwide attributable to selected environmental risk factors including deaths per country per year as a result of outdoor air pollution.[5]

Worries that air pollution may have significant effects on health have recently been fuelled by publication of new evidence linking low levels of ambient air pollution with small public health effect. In order to suffer health effect, an individual who exposed to a pollutant

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and the pollutant must be able to reach those parts of the body that are vulnerable to its effect.

Because of the blockade as a result of disputed occupation of the Gaza governorates, and the large quantities of rubbles from building that destroyed by Israel bombardments during wars 2008, 2012, and 2014. The Palestinian owners of crushers plants using homemade crushers, was the only way to rebuild what was destroyed by the occupation in Gaza governorates.

The researchers attempt to measure the concentration of PM_{10} in crusher's plants during operation and to examine effects on the complete blood counts that have occurred as a result of direct exposure of workers to particulate matter air pollution for contentious long hours of work. Due to that there is limited available data about the complete blood counts effects that caused to crushers workers, and limited available data associated with concentration of PM_{10} in crushers plants.

MATERIALS AND METHODS

The general objective of this study is to evaluate the level of PM_{10} air pollution in crushers plants, and their effects on complete blood count for crusher workers.

The target population of the study were (87) individuals. Case (exposed) group were 40, and control (non-exposed) group were 47. This case-control study was conducted between the participants who are under age of 15-65 and have no medical history and who works in crushers at Middle Governorate, and the participants those who are under the age of 15 years or more than 65, and have past medical history and do not work in the Middle Governorate were considered.

This case-control study was conducted during the period from April-August 2013 in gravel crushers, at Middle Governorate, Southern Governorates, Palestine.

Case Group (Exposed)

All workers in the six crushers at Middle Governorate who accomplished criteria, the number of workers is 40, as they worked in gravel crushers and continuously exposed to dust without using any protective devices, the exposed workers were male, their age ranged from 15-65 years, and does not have any past medical history.

Control Group (Non-exposed)

The control group contain 47 individuals who live in the same area of case group, their ages ranged from 15-65 years, do not have any past medical history, but they do not work in the gravel crushers.

Field and Laboratory Equipment

1. Hematology analyzer: A hematology analyzer is an instrument used to perform a complete blood count or full blood count (CBC or FBC).
2. HAL-HPC300 handheld optical particle counter.
3. PM_{10} measuring device were used for all crushers plants.

RESULTS

This study conducted on all crushers and workers who continuously exposed to dust without using any protective devices in the Middle Governorate which has six crushers distributed on all areas. (Figures 1-3)

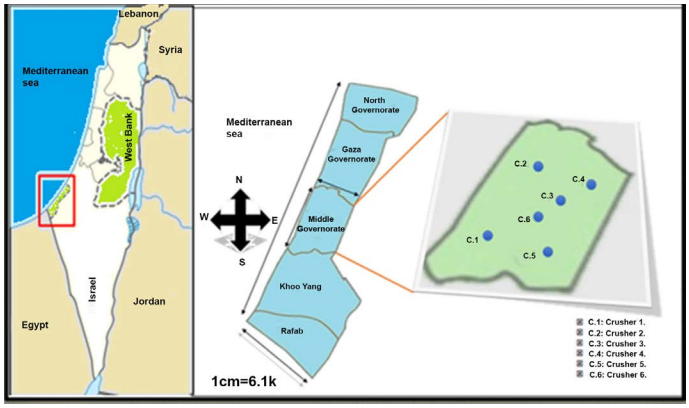

Figure 1: The geographical distribution of crushers in Middle Governorate.

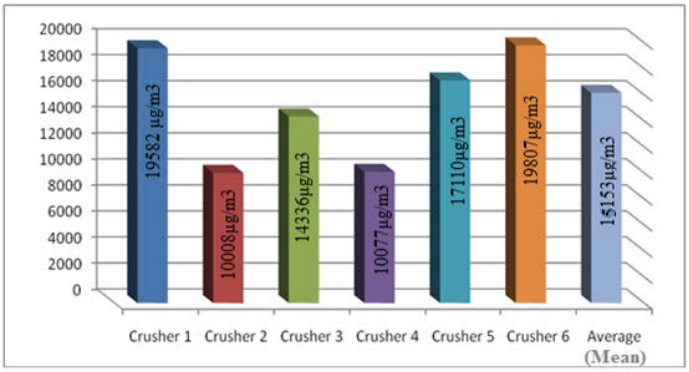

Figure 2: Concentrations of PM_{10} that emitted from six crushers and the average of these concentrations. PM_{10} air pollution monitoring data for the six crushers

As shown in Figure (2) reveals that the emission of PM_{10} by the crushers varies widely from 10008 to 19807 µg/m^3, with an average particulate matter contribution of 15153 µg/m^3, which is about more than 100 times higher than the particulate matter (PM_{10}) existing daily average standard of 150 µg/m^3.[6-8]

The results in Figure (3) show the percentage of ages for both cases and control groups. Furthermore, it shows the elevated level of ages rapprochement between the two groups, which increase the accuracy of the study.

Results of Complete Blood Counts between Case Group (40) and Control Group (47) are shown in Table 1.

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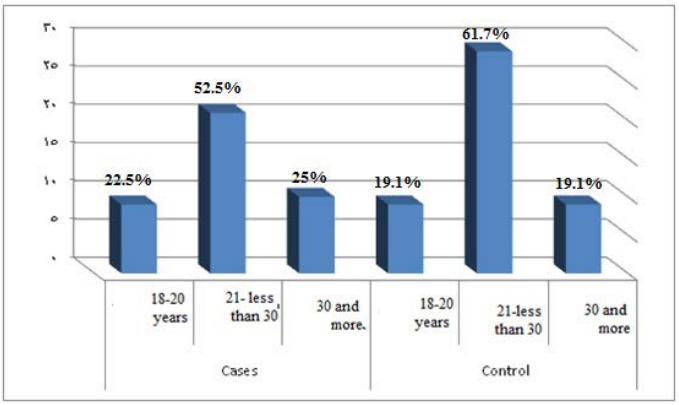

Figure 3: Age of cases and control groups.

CBC results	Groups	N	Mean	SD	T-Test value	P-value
RBCS	Case	40	5.04	0.51	-1.260	0.211
	Control	47	5.17	0.44		
WBCS	Case	40	8.67	1.24	6.975	0.000
	Control	47	7.22	0.64		
HGB	Case	40	14.75	0.92	-1.170	0.245
	Control	47	14.97	0.81		

Table 1: The results of independent samples T-test for complete blood counts results between (40) case group and (47) control group.

Red blood cells (RBCs): The mean of RBCs for case and control group is (5.04, with SD of 0.51) and (5.17, with SD of 0.44), respectively. The value of the T-test equals -1.260, with p-value equals 0.211. This means that there is sufficient evidence to conclude that mean of RBCs is insignificantly different between the two groups. In other words, there is insignificant difference in the mean RBCs between case and control group.

White blood cells (WBCs): The mean of WBCs for case and control group is (8.67, with SD of 1.24) and (7.22, with SD of 0.64), respectively. The value of the T-test equals 6.975, with p-value equals 0.000. This reveals that there is an evidence to conclude that mean of WBCs is significantly different between the two groups. Since the sign of the T-test is positive, then mean of WBCs for case group is significantly greater than control group.

Hemoglobin (HGB): The mean of HGB for case and control group is (14.75, with SD of 0.92) and (14.97, with SD of 0.81), respectively. The value of the T-test equals -1.170, with p-value equals 0.245. This implies that there is sufficient evidence to conclude that mean of HGB is insignificantly different between the two groups. In other words, there is insignificant difference in the mean HGB between case group and control group.

DISCUSSION

Positive relationship is observed between PM_{10} air pollution and increasing White Blood Cells (WBCs) (leukocytosis) in this study. The statistical strength of relationship between PM_{10} air pollution exposure and increasing WBCs is in line with the study conducted by Tan, et al.[4] have demonstrated leukocytosis in young military recruits exposed to an acute episode of particles air pollution during forest fires of south east Asia in the summer of 1997, suggesting that an episode of acute exposure to PM_{10} air pollution causes bone marrow stimulation in humans.[2]

Furthermore, Van and Tem studies showed that an acute exposure of PM_{10} air pollution causes leukocytosis in humans and proinflammatory cytokines in the blood collect in the south east Asia.[2]

This is supported by other independent longitudinal studies linking elevation of the peripheral blood count to increase mortality during exposure of PM_{10} air pollution. In consistent, Wells, et al. have shown that an increase in leukocyte count is predictor of total mortality, independent of smoking in large population-based studies[9]

Examination Survey in the United States, conducted among adults aged 20-89 years, which showed significant association between WBC count and estimated local PM_{10} levels during 1 year.[3,10] Also, our findings are consistent with animal experiments showing an increase release of WBCs and their precursors from the bone marrow in response to the deposition of particles in the lungs.

These findings suggest that inflammatory mediators released from lung are capable of irritating not only a local inflammatory response, but also a systematic response when PM_{10} are deposited in the lungs, resulting in leukocytosis.

In the present study, it observed significant relationship between PM_{10} air pollution and increasing WBCs, these results are consistent with physiologic and related studies results. Insignificant relationships are observed between PM_{10} air pollution and hemoglobin and red blood cells.

A cross-over study among 29 participants with or without biking exercise and exposed to particulate air pollutants did not find any significant association of particulate air pollutants with hemoglobin, RBC and platelet count and markers of inflammation in healthy adolescents and childs.[11]

The associations of particulate air pollutants with hematologic parameters are consistent with the chronic effects of air pollutants on hematological factors.[1]

In the present study, it shows insignificant relationship due to the short duration of exposure to PM_{10} for target groups (1-3) years compared with appearance of significant impact on hemoglobin and red blood cells, which need long term period to appear clearly.

In summary, our findings are consistent with the results of studies that have mentioned and other, which showed positive

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and significant relationship between exposure of PM_{10} air pollution and increasing white blood cells (leukocytosis).

CONCLUSION

The particulate matter that emitted from the crushers varies widely from 10008 to 19807 $\mu g/m^3$, with an average particulate matter contribution of 15153 $\mu g/m^3$, which is about more than 100 times higher than the particulate matter (PM_{10}) existing standard.

Increasing in white blood cells count reported in this study among the exposed workers. This increasing was found to be related to exposure of PM_{10} air pollution, as a result of the inflammatory process.

Data analysis shows insignificant relationship between (Red blood cells and Hemoglobin) and PM_{10} air pollution exposure, due to the short duration of exposure to PM_{10} for target groups (1-3) years compared with appearance of significant impact on hemoglobin and red blood cells, which need long term period to appear clearly.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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CONSENT

The authors has received written permission for publication of the case details.

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Short Communication

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Is *Mycoplasma Pneumoniae* Infection Associated with Adult Asthma Exacerbation?

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Mycoplasma pneumoniae infection has been considered as a cause of initial onset of bronchial asthma[1] or exacerbation of asthma.[2] For example, Kraft, et al. showed that *M. pneumoniae* was detected by Polymerase Chain Reaction (PCR) in 10 of 18 asthmatics and one of 11 control subjects ($p<0.02$).[3] Furthermore, Martin, et al. reported that thirty-one of 55 asthmatic adult patients were PCR-positive for *Mycoplasma* (n=25) or *Chlamydia* spp. (n=6) compared with 1 of 11 (9%) control patients.[4] In both of those studies, *M. pneumoniae* was confirmed primarily in lung biopsy specimens or in lavage fluid.[3,4]

We performed comprehensive analysis for multiple pathogens, including *M. pneumoniae*, *Chlamydophila pneumoniae*, and common respiratory viruses (i.e., Respiratory Syncytial Virus (RSV), Human rhinovirus (HRV), Human metapneumovirus (HMPV), influenza virus, human parainfluenza virus, human bocavirus) using PCR or real-time PCR techniques. However, our preliminary data, obtained for both outpatient (n=29) and inpatient (n=15) subjects suffering from asthma attacks, did not detect *M. pneumoniae or C. pneumoniae* in the nasopharyngeal or oropharyngeal swabs from these individuals.

In contrast, real-time PCR detected virus in 6.9% (n=2) and 46.7% (n=7) of subjects with asthma exacerbations in outpatient and inpatient settings, respectively.[5] The incidence of virus-positive viral status was significantly higher in the latter group ($p<0.002$).[5] This observation was similar to the results obtained in a previous study that, using PCR-based viral diagnostics, detected viral respiratory infections in up to 50% of adults with asthma exacerbations.[6]

Notably, in a total of 15 hospitalized patients, 7 virus-positive cases (n=5, HRV; n=1, HMPV; n=1, RSV) had significantly lower values of SpO_2 (81.4±3.9%) than those measured in the virus-negative group (n=8, SpO_2: 91.8±1.3%, $p<0.007$), and the frequency of hypercapnea ($PaCO_2$>45 Torr) was significantly higher in the virus-positive group (66.7%, n=4) than in the virus-negative group (0%; $p= 0.014$).[5]

Thus, in the context of social and economic costs, our preliminary data suggest that viral infection in asthmatic patients may be more important for case management than is *M. pneumoniae* infection in these patients. Larger studies will be needed to further address the role of *M. pneumoniae* in the exacerbation of asthma.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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Illustration

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Rapid Diagnosis of Hemosiderin-Laden Macrophages With Diff-Quick Stain

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KEYWORDS: Hemosiderin-laden macrophages; Alveolar hemorrhage; Rapid diagnosis; Diff-quick stain; Hemosiderin.

A 77-year-old healthy woman was referred to our hospital with sudden hemoptysis. Chest X-ray showed moderate consolidation in the right upper lung fields. On hospital day 3, urgent bronchoscopy was performed and sequential Bronchoalveolar lavage (BAL) fluid obtained from segment 2 of the right lung was progressively more hemorrhagic**.** Of note, cytological evaluation with rapid Diff-quick stain demonstrated the presence of numerous large Alveolar Macrophages (AMs) engulfing yellow-colored material (Figures 1A and 1B; arrows), so-called Hemosiderin-laden macrophages together with abundant red blood cells in the background. On Papanicolaou staining, intracytoplasmic hemosiderin accumulation in the AMs was seen as faint, brown-colored, dense deposits (Figure 1C). She was thus tentatively diagnosed with idiopathic alveolar hemorrhage. Hemosiderin-laden macrophages are a hallmark of alveolar hemorrhage, which usually takes a few days to diagnose,[1,2] but this case clearly demonstrated that these cells can be seen even in a rapid diagnostic test with Diff-quick stain.

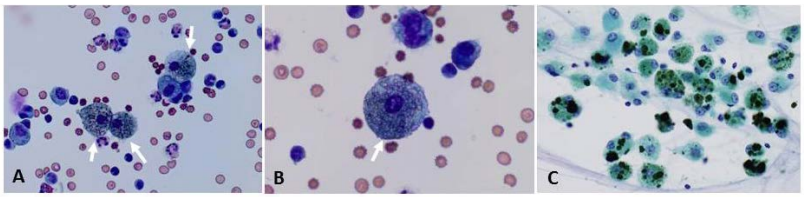

Figure 1: A and B. Cytological evaluation with rapid Diff-quick stain demonstrated the presence of numerous large Alveolar Macrophages (AMs) engulfing yellow-colored material. C. On Papanicolaou staining, intracytoplasmic hemosiderin accumulation in the AMs was seen as faint, brown-colored, dense deposits.

CONFLICTS OF INTEREST

The authors declare no conflict of interest associated with this manuscript.

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