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# Diagnosis of hypersensitivity pneumonites in non smokers by thoracoscopic cryobiopsy: Changing concept of BAL lymphocytosis

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**Abstract**
Bronchoalveolar lavage (BAL) is the most sensitive procedure to detect an alveolitis in patients suspected of having EAA, but is not always necessary, particularly in patients with exposure history and typical confident distinction of chronic HP from IPF and NSIP only about 50 percent of the time [6]. Patients and methods; Retrospective study of 30 non smokers patients finally diagnosed as EAA, FOB and BAL was taken from all patients and net result of it less than 20%, natural challenge test then thoracoscopic cryobiopsy taken for final diagnosis
**Results:** Patients age range from 24 to 50 years, most of patients were female 83.3%, 80% were exposed to birds and remaining 20% are farmers. Duration of illness ranged from 4 to 24 months, all patients suffering from SOB, and cough, natural challenge were positive in 100% of cases, HRCT were nodular in 20%,and reticulo-nodular in 80%, biopsy were diagnostic to all patients. BAL lymphocytes ranged from 8% to 12%, mast cell median 5%and neutrophils was 3% FEV1 median of FEV1 was 45% and FVC 50%, and DLCO was 42%, all patients were restrictive in relation to function.

**Keywords:** Hypersensitivity pneumonitis, BAL, lymphocytosis

## Introduction
Hypersensitivity pneumonitis (HP), also called extrinsic allergic alveolitis, is a complex syndrome of different intensity, clinical presentation, and natural history, rather than a single, uniform disease [1-2].
Few years ago, clinically the presentations of HP have been divided into acute, subacute, or chronic according to the frequency, duration, and intensity of exposure and upon the duration of disease [3, 2-4],
Other authors were classified HP into two categories: acute/inflammatory and chronic/fibrotic [5].
however the classification of acute, subacute, and chronic HP has limitations, these categories highlight the potential variations in presentation of HP [2].
Bronchoalveolar lavage (BAL) is the most sensitive to detect an alveolitis in patients suspected of having HP, but is not always necessary, particularly in patients with a sure exposure history and typical confident distinction of chronic HP from IPF and NSIP only about 50 percent of the time [6].
High resolution computed tomography (HRCT) findings A marked BAL lymphocytosis (greater than 20 percent and often exceeding 50 percent of the white blood cells recovered) is a nonspecific, but helpful, finding when the clinical and radiographic findings suggest subacute HP [11, 7]. Patients who smoke cigarettes tend to have a lower BAL lymphocyte count (>20 percent) compared with nonsmokers (>30 percent) [9]. BAL lymphocytosis can also be seen in organizing pneumonia and nonspecific interstitial pneumonia, but not usually at this high level.
The majority of patients with chronic HP have BAL lymphocyte counts >20 percent, some patients with chronic HP have normal or low lymphocyte numbers [5, 11, 8]. A longer duration of time since last exposure can cause a lower BAL lymphocyte count [10].
The role of transbronchial biopsies during flexible bronchoscopy remains questionable. The centrilobular distribution of HP (except in chronic fibrotic disease) can increase the yield

relative to other interstitial diseases, although the small size of these biopsies may be insufficient for a sure diagnosis. In contrast, video-assisted surgical biopsy yields larger samples and enables sampling from more than one lobe. Selecting among these options is done on a case-by-case basis; a multidisciplinary team can help guide decision-making [11]

We aimed in this retrospective study to change the concept of BAL lymphocytosis in diagnosis of EAA

## Patients and methods

Retrospective study of 30 non smokers patients finally diagnosed as EAA including all patients in last 5 years in Mansoura University Hospital Chest Medicine department, IRB number was (20.10.1047 R1) all patients have BAL less than 20%, lung biopsy were done to all patients by cryo biopsy through medical thoracoscopy, complete history taking, clinical examination compatible with EAA, CT finding were done and all patients were reticular or reticulo-nodular (centrilobular) and were predominant to upper lung zone, natural challenge test was done to all patients, FOB done and BAL taken from all patients, and cryobiopsy through medical thoracoscopy were done.

### Natural challenge test

Re-exposure of the patient to the environment of the suspected allergen is sometimes used to demonstrate a relationship between symptoms and a this agents, and thus support the diagnosis of HP [12-13]. fever, malaise, headache, crackles on chest exam, peripheral neutrophilia, and decreased forced vital capacity (FVC) occur 8 to 12 hours after exposure. Hypoxemia and radiologic abnormalities (increase in ground glass opacities or nodularity) may occur in severe reactions. Consequently, the patient monitored closely for at least 24 hours

### FOB and BAL

Flexible bronchoscopy was done at the Bronchoscopy Unit, Mansoura university, Egypt, using bronchoscope (Pentax EB-1970 TK) manufactured by Pentax company Tokyo, Japan. After intravenous sedation of 10 mg of diazepam, introduction of the bronchoscope to the middle lobe and instillation of 60 ml normal saline then aspirated, rapid transference to clinical pathologiest for differential cell count by flow cytometery

### Cryo-biopsy through medical thoracoscopy

Introduction of the rigid thoracoscope:

An incision was made with a scalpel in mid axillary line through skin and subcutaneous tissue appropriate to the size of the trocar to be used. Induction of pneumothorax was done by veress needle at the time of procedure on table. While fixation of the intercostal space; the trocar was introduced with forceful corkscrew motion until release of the resistance of the internal thoracic fascia. The trocar should lie at 0.5 cm within the pleural space. Then the trocar was removed and the telescope rodlens was inserted through the cannula into pleural space.

### Lung biopsy maneuver

Cryo probe which set at - 80 co2 we scratch the surface of visceral pleura and apply the cryo by pressure over foot pedal for 15 seconds then defrost for 3 cycles to decrease incidence of bleeding, forth cycle applied for 10 second then we pulled the probe.

### Statistical analysis

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 15 for Windows® (SPSS Inc, Chicago, IL, USA). Qualitative data was presented as numbers and percents. Normally distributed data was presented as mean and standard deviation (SD). Non-parametric data was presented as median (min – max).

## Results

**Table 1:** Demographic characteristics and exposure history of the participants in the study

| | | All patients (n= 30) | | | | |
|---|---|---|---|---|---|---|
| | | **Mean & SD** | **Median** | **Minimum** | **Maximum** | **IQR** |
| Age | | 34.97 ± 6.294 | 34.00 | 24 | 50 | 29.75, 39.25 |
| Gender | Male | 16.7% (5) | | | | |
| | Female | 83.3% (25) | | | | |
| History of exposure | Birds | 80% (24) | | | | |
| | Farmer | 20% (6) | | | | |
| Data is expressed as mean and standard deviation, median, Minimum, Maximum and Inter-quartile range or as percentage and frequency. | | | | | | |

Patients age range from 24 to 50 years, most of patients were female 83.3%, 80% were exposed to birds and remaining 20% are farmers.

**Table 2:** Disease duration, clinical, radiological and pathological examination of the studied patients:

| | | All patients (n= 30) | | | | |
|---|---|---|---|---|---|---|
| | | **Mean & SD** | **Median** | **Minimum** | **Maximum** | **IQR** |
| Duration | | 10.00 ± 5.837 | 8.00 | 4 | 24 | 6.00, 12.00 |
| SOB | | 2.63 ± 0.556 | 3.00 | 2 | 4 | 2.00, 3.00 |
| Cough | | 100% (30) | | | | |
| Natural challenge | | 100% (30) | | | | |
| Crepitations | | 83.3% (25) | | | | |
| Xray | Nodular | 50% (15) | | | | |
| | Reticulation | 50% (15) | | | | |
| CT | Nodular | 20% (6) | | | | |
| | Reticulation | 80% (24) | | | | |
| EAA in cryobiopsy | | 100% (30) | | | | |
| Data is expressed as mean and standard deviation, median, Minimum, Maximum and Inter-quartile range or as percentage and frequency. | | | | | | |

Duration of illness ranged from 4 to 24 months, all patients suffering from SOB, and cough, natural challenge were positive in 100% of cases, HRCT were nodular in 20%,and reticulo-nodular in 80%, biopsy were diagnostic to all patients

**Table 3:** Laboratory investigations of the studied patients

| | All patients (n= 30) | | | | |
|---|---|---|---|---|---|
| | **Mean & SD** | **Median** | **Minimum** | **Maximum** | **IQR** |
| HB | 10.47 ± 1.074 | 10.00 | 9 | 13 | 10.00, 11.00 |
| Platelets | 185.03 ± 40.614 | 190.00 | 25 | 250 | 163.50, 210.00 |
| WBCS | 6.93 ± 1.172 | 7.00 | 5 | 9 | 6.00, 8.00 |
| INR | 1.07 ± 0.071 | 1.10 | 1 | 1 | 1.00, 1.10 |
| ESR | 8.67 ± 3.457 | 10.00 | 5 | 15 | 5.00, 10.00 |
| FEV1 | 44.60 ± 4.073 | 45.00 | 33 | 50 | 42.75, 47.25 |
| FVC | 48.40 ± 4.658 | 50.00 | 36 | 55 | 46.75, 51.25 |
| FEV1% | 89.77 ± 1.716 | 90.00 | 88 | 95 | 88.00, 90.25 |
| DLCO | 41.63 ± 2.659 | 42.00 | 37 | 50 | 39.00, 44.00 |
| BAL lymphocytes | 8.30 ± 2.277 | 8.00 | 5 | 12 | 7.00, 10.00 |
| BAL mast cells | 4.60 ± 1.303 | 5.00 | 2 | 8 | 4.00, 5.00 |
| BAL neutrophils | 2.67 ± 1.583 | 3.00 | 1 | 5 | 1.00, 4.00 |
| Data is expressed as mean and standard deviation, median, Minimum, Maximum and Inter-quartile range. | | | | | |

BAL lymphocytes ranged from 8% to 12%, mast cell median 5%and neutrophils was 3% FEV1 median of FEV1 was 45% and FVC 50%, and DLCO was 42%, all patients were restrictive in relation to function

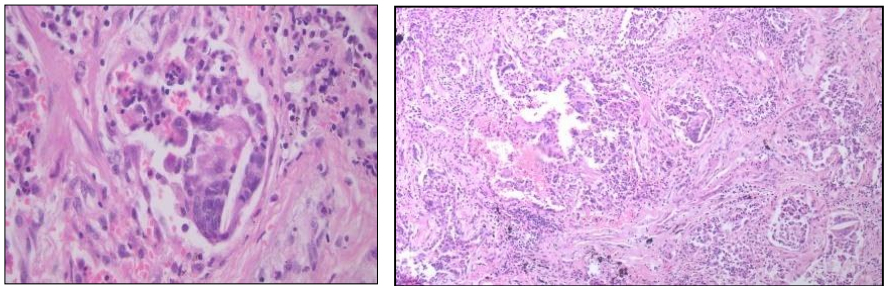

**Fig 1:** Microscopic examination showed focal involvement of lung tissue by interstitial inflammation with mild fibrosis. It is formed of lymphocytes, plasma cells, eosinophils and histiocytes. Scattered multinucleated giant cells and cholesterol clefts are seen. The alveolar lining is hyperplastic.

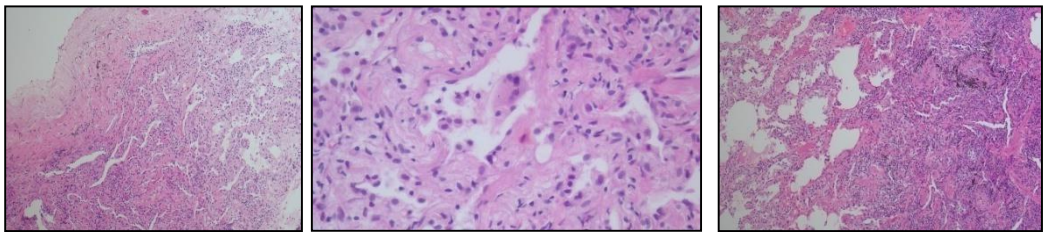

**Fig 2:** Microscopic examination showed focal involvement of lung parenchyma with interstitial inflammation. It is formed of lymphocytes, plasma cells and histiocytes. Scattered macrophages and small multinucleated giant cells are seen.

## Discussion

We studied 30 patients with history of exposure, natural challenge positive, and radiology compatible with HP (centrilobular nodules), BAL lymphocytes were between 5 - 12%. we have criteria of probable cases, so lung biopsy were done.

Age of our patients ranged from 24 to 50 years and most of them were females 83.3% and all of them were non smoker 80% have history of exposure to birds while 20% are farmers. Aramia *et al.* 1992 was concluded that smoking had a suppressive effect to develope HP, but smoking does not have further suppression after the disease was established [14]. Murin *et al.* 2000 study the general effect of smoking on respiratory diseases and conclude that its effect is hazardous, but in the cases of sarcoidosis and hypersensitivity pneumonitis smoking may actually be associated with suppression of disease appearance [15]. Solymani *et al.* 2007 conclude that the incidence of EAA in the UK population appears to be stable overtime, and suggests about 600 new cases of EAA each year. People with EAA are not smoker than the general population [16]. Lalancette *et al*. 1993 and Bourke *et al.* 2001 reported that Farmer's lung is a commonest forms of HP, affecting 0.4 to 7 percent of the farmers [17, 18].

In the present study Duration from onset of symptoms till diagnosis of disease ranged from 4 to 24 months,cough and dyspnea is the common symptoms and crepitation present in 83.3%. CT finding was reticular in 80% and nodular in 20%. Subacute HP is characterized by the gradual development of productive cough, dyspnea, fatigue, anorexia, and weight loss. Similar findings may occur in patients who suffer repeated, infrequent acute attacks of HP characterized by cough and malaise [19]. Patients with chronic HP usually report the gradual onset of cough, dyspnea, fatigue, and weight loss, and may lack a history of acute episodes. Digital clubbing may be seen in advanced disease and associated with rapid progression [20].

In the present study pulmonary function was restrictive FEV1% was 89.77 ± 1.716, FEV1was 44.60 ± 4.073, FVC was 48.40 ± 4.658 and DLCO was 41.63 ± 2.659. Morrel *et al.* 2008 discuss that PFT of HP were Restrictive ventilatory impairment in the most frequent functional pattern (77%), although 9% and 4% showed a pure obstructive and mixed pattern, respectively.

In the present study thoracoscopic cryobiopsy has diagnostic yield 100%, Adams *et al* 2018 conclude that TBBX and BAL significantly increased the diagnostic yield inspite of the BAL lymphocyte alone. The yield of bronchoscopy with TBBX and BAL associated with a lymphocyte count > 40% was used as a cutoff was 52%. [23]. Sheth *et al*. 2017 conclude that TBB, when added to clinical and HRCT data, may provide enough information to make a confident and accurate diagnosis in approximately 20% to 30% of patients with ILD [24]. lentz *et al.* 2018 reported that the diagnostic yield of diffuse parenchymal lung disease (DPLD), in which the reported 70% to 80% by use of bronchoscopic cryoprobe [25]. Iftikhar 2017 reported that the diagnostic yield, sensitivity, and specificity of transbronchial lung cryobiopsy were 83.7% (76.9-88.8%), 87% (85-89%), and 57% (40-73%), respectively. The diagnostic yield, sensitivity, and specificity of VATS were 92.7% (87.6-95.8%), 91.0% (89-92%), and 58% (31-81%), respectively [26].

Our result of BAL lymphocytes between 5%: 12%. Burek *et al.* 2001 conclude that a normal lymphocyte BAL count exclude all but residual disease [18], but an alveolar lymphocytosis is not specific to HP [21].

Cailloud *et al.* 2012 A multicentric study was conducted on 139 patients who fulfilled the diagnostic criteria of HP, mainly affected by farmer's lung. Mean total cell count in BAL fluid was 594 ± 401.10 [3] cells /ml. Prominent absolute lymphocytic alveolitis, moderate neutrophilia, and mild eosinophilia and mastocytosis were found [22]. conclusion and recommendations: thoracoscopic cryobiopsy has excellent diagnostic yield of EAA. Normal or less than 20% lymphocytes can not rolled out diagnosis of EAA, and BAL lymphocytes need future assessment in all stages of disease.

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