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Eosinophilic bronchiolitis: is it a new syndrome?

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Identification of new diseases or of a cluster (syndrome) of disorders with very similar pathological, radiological and clinical aspects even sharing common pathogenic steps is an important fact to build up the scientific soul of the complex and intriguing art called medicine. In literature, a new distinct syndrome, the hyperesinophilic obliterative bronchiolitis, is described by Cordier JF et al [1]. This syndrome is defined by three criteria: 1) blood eosinophil cell count > 1G/L (and/or BAL eosinophil differential cell count > 25%); 2) persistent airflow obstruction on lung function tests not modifiable after 4-6 weeks of inhaled corticosteroid therapy (2,000 micrograms/day of beclometasone or equivalent); 3) lung biopsy showing inflammatory bronchiolitis with prominent bronchiolar wall infiltration by eosinophils and/or characteristic direct HRCT features of bronchiolitis (poorly defined centrilobular nodules, branching opacities, tree in bud pattern). The first impression that a cursory Clinician and/or Pathologist has, going swiftly through this list of criteria, is that "we are dealing with a severe and persistent form of asthma". In chronic asthma the obstructive impairment becomes fixed and not modifiable -at least easily- with steroids or bronchodilators; in chronic asthma eosinophils in lung tissue and blood may be constantly increased and HRCT shows abnormalities in between 68% and 90% of patients (bronchial wall thickening and narrowing of bronchial lumen, cylindric bronchiectasis, thick linear opacities, areas of decreased attenuation, bronchial mucoid impaction, small centrilobular opacities, airspace consolidation, thin-walled cysts) [2]. Finally, from a pathological point of view, mucous eosinophilic plugs may fill both small bronchi and bronchioles, and marked goblet cell hyperplasia/metaplasia of bronchial/bronchiolar epithelium, thickening of the basement membrane, bronchiolar smooth muscle hypertrophy, fibrosis of the bronchiolar wall with peribronchiolar lymphoid aggregates, mixed inflammatory infiltrate with prominent eosinophils throughout airway walls are all detectable [3]. However it is clear that the concept of "severe and persistent asthma" is still poorly understood and the contribute of these Authors [1] may help to better define and appreciate the characteristics (clinical, radiographic, pathologic and biologic) of those patients that have symptoms, signs, imaging findings and even pathologic aspects as bounderies between "severe asthma" and some form of a not yet well defined bronchiolitis.

In the reported series [1] one patient had a limited form of Churg Strauss syndrome, one patient showed an aberrant population of T lymphocytes in the peripheral blood (CD3+CD4+CD7- lymphocytes) with oligoclonal T-cell receptor gamma VG9J1J2 re-arrangement suggesting a relationship with the lymphocytic variant of hypereosinophilic syndrome [4], one patient had the typical aspects of Allergic Bronchopulmonary Mycosis (as *Aspergillus* was not documented either by immunologic tests , microbiology or histology, a diagnosis of ABPA may not be substained) [3] and, finally, in one patient -not included in the present series but part of the clinical experience of

the Authors- the lesion was allegedly related to minocycline use. Almost all the patients had airflow obstruction despite inhaled therapy; HRCT scan features indicated that the lesions were centered on small bronchi/bronchioles (bronchial wall thickening, "tree in bud" pattern, mucoid impaction, "finger in glove" pattern, centrilobular nodules), the burden of eosinophilic infiltrate in the airway walls was higher that expected in asthma and rather typical of cellular bronchiolitis [5]; finally in two patients bronchoscopy documented patchy tracheobronchial mucosal lesions corresponding histopathologically to ulcerated areas of necrosis and prominent eosinophilic inflammation; paranasal sinus inflammation was well documented in 4 out of 6 patients confirming that the lesions extended also to the larger respiratory airways. Improvement was observed after oral steroids or even immunosuppressor drugs use.

The box - having as selective criteria direct CT scan findings indicating small airways disease, eosinophilic bronchiolitis and blood/BAL eosinophilia- inside which the "hypereosinohilic obliterative bronchiolitis syndrome" might be included, contains other entities or specific subset of patients.

In Churg Strauss syndrome, it is already known that occasionally eosinophilic inflammatory lesions may primarly involve the bronchovascular bundles with minimal spread to the alveolar parenchyma [6] and bronchoscopy may detect lesions even in larger airways. Eosinophilic bronchiolitis was reported by Japanese Authors [7]: common characteristics included bronchiolitis with eosinophilic infiltration, CT scan findings similar to that observed in diffuse panbronchiolitis, ventilatory impairment, airway hyper-reactivity, and blood and BAL-fluid eosinophilia. Recently Wenzel SE et al [8] described 10 patients with clinically severe asthma with subtle CT scan lesions (only in one patient a "tree in bud pattern" was detected) and with characteristic pathologic aspects: peripheral airways showing asthmatic changes (submucosal inflammation consisting of eosinophils, neutrophils, lymphocytic transmigration, submucosal fibrosis, mucus plugging, peribronchiolar fibrosis, bronchioloectasis, muscular hypertrophy along with interstitial mononuclear pneumonia with the presence of poorly formed granulomas, lymphoid aggregates and airspace organization). The Authors [8] labeled this subset of patients as "asthmatic granulomatosis". Interestingly, non steroidal cytotoxic drugs improved the course of the disease. The description and data collected by Cordier et al [1] add therefore some other elements of knowledge to this not yet well defined ensemble: some patients had an autoimmune disorder (Churg Strauss syndrome), an hypersensitivity behaviour (allergic bronchopulmonary mycosis), some had a disregulation of T lymphocytes (probably including lymphocytes expressing and releasing IL-5), and some other had elements indicating a drug reaction. Therefore hypereosinophilic obliterative bronchiolitis along with other recently reported "entities" indicate that patients usually considered as affected by

"severe asthma" may actually have a disorder in which different biologic processes are involved but which share common elements:

1. small airways are the anatomic zone more heavily involved (although the infiltrate may extend to the large airways and paranasal sinuses)
2. eosinophils are more represented cells in the morphologic lesion
3. dis-regulation of immunity (autoantibodies production, hypersensitivity, disregulation of T cells) may have a role
4. non steroidal immunosuppressant drugs might be effective (confirming the empirical feeling of expert Clinicians).

This report could open new windows drawing attention to the links between autoimmunity, hypersensitivity, T cell dis-regulation, eosinophilic inflammation and bronchiolitis; it raises interest in new pathogenetic mechanisms leading to obliterative bronchiolitis, discloses links between oligoclonal T cell proliferation and bronchiolocentric eosinophilic inflammation, suggests that cytotoxic drugs or even monoclonal antibodies might have some benefit. Next step to exploit these new scenarios could be the collection of a significant number of patients with these clinical - radiological characteristics provided with pathological (and biological) data. In fact in only two patients the Authors [1] reported histopathological information. Interestingly, as the lesions are centrilobular, a bronchoscopic approach (transbronchial lung biopsy with common flexible forceps, jumbo forceps or even cryoprobes) could obviate the need of a surgical approach. In conclusion the study by Cordier JF et al [1] reminds us that a good clinical reasoning is at the basis of a well oriented research in medicine.

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